CHRONIC TOXICITY SUMMARY

NAPHTHALENE

(naphthene, NCI-C5290, albocarbon, dezodorator, moth balls, moth flakes, tar camphor, white tar, naphthalin, naphthaline)

CAS Registry Number: 91-20-3

I. Chronic Toxicity Summary

Inhalation reference exposure level	**9 μg/m^3 (2 ppm)**
Critical effect(s)	Respiratory effects (nasal inflammation, olfactory epithelial metaplasia, respiratory epithelial hyperplasia) in mice
Hazard index target(s)	Respiratory system, blood systems

II. Physical and Chemical Properties (HSDB, 1995)

Description	White crystalline powder
Molecular formula	$C_{10}H_8$
Molecular weight	128.6 g/mol
Specific gravity	4.42 @ 20ºC
Boiling point	218ºC
Melting point	80.5 ºC
Vapor pressure	0.087 mm Hg
Conversion factor	5.26 μg/m^3 per ppb at 25ºC

III. Major Uses or Sources

Naphthalene is a natural constituent of coal tar (approximately 11%) (HSBD, 1995). Naphthalene is used as a moth repellent, though this use is decreasing in favor of p-dichlorobenzene (HSDB, 1995). It has also been used in the manufacture of phthalic anhydride, phthalic & anthranilic acids, naphthols, naphthylamines, 1-naphthyl-n-methylcarbamate insecticide, beta-naphthol, naphthalene sulfonates, synthetic resins, celluloid, lampblack, smokeless powder, anthraquinone, indigo, perylene , and hydronaphthalenes (NTP, 1992; HSDB, 1995).

IV. Effects of Human Exposure

Nine persons (eight adults and one child) were exposed to naphthalene vapors from several hundred mothballs in their homes. Nausea, vomiting, abdominal pain, and anemia were reported (Linick, 1983). Testing at one home following the incidence indicated an airborne naphthalene concentration of 20 ppb. Symptoms abated after removal of the mothballs.

Workers occupationally exposed to naphthalene fumes or dust for up to five years were studied for adverse ocular effects (Ghetti and Mariani, 1956). Multiple pin-point opacities developed in 8 of 21 workers. Vision did not appear to be impaired.

Cataracts and retinal hemorrhage were observed in a 44 year old man occupationally exposed to powdered naphthalene, and a coworker developed chorioretinitis (van der Hoeve, 1906).

Wolf (1978) reported that a majority of 15 persons involved in naphthalene manufacture developed either rhinopharyngolaryngitis and or laryngeal carcinoma.

Ingestion of naphthalene or p-dichlorobenzene mothballs is a frequent cause of accidental poisoning of children (Siegel and Wason, 1986). Infants exposed to naphthalene vapors from clothes or blankets have become ill or have died (U.S. EPA, 1990). The effects in infants have been associated with maternal naphthalene exposure during gestation (U.S. EPA, 1990).

Deaths have been reported following ingestion of naphthalene mothballs. A 17-year old male ingested mothballs; developed gastrointestinal bleeding, hematuria, and coma; and died after five days (Gupta *et al.*, 1979). A 30-year old female ingested 30 mothballs and died after five days (Kurz, 1987).

Acute hemolytic anemia was reported among 21 infants exposed to naphthalene vapors from nearby mothball-treated materials (Valaes *et al.*, 1963). Increased serum bilirubin, methemoglobin, Heinz bodies, and fragmented red blood cells were observed. Kernicterus was noted in eight of the children, and two of the children died. Ten of these children had a genetic deficiency in glucose-6-phosphate dehydrogenase.

A 12-year old male ingested 4 g of naphthalene and 20 hours later developed hematuria, anemia, restlessness, and liver enlargement (Manchanda and Sood, 1960). The patient recovered after 8 days.

A 69-year old female developed aplastic anemia two months after several weeks exposure to naphthalene and p-dichlorobenzene (Harden and Baetjer, 1978).

V. Effects of Animal Exposure

Male and female B6C3F1 mice were exposed to naphthalene (>99% pure) vapor for 6 hours per day, 5 days per week over 104 weeks (NTP, 1992). Concentrations used were 0 (150 mice), 10 (150 mice), or 30 ppm (300 mice) naphthalene. (Table 1). Lesions were observed in the nose and lungs of exposed mice, including increased incidences of chronic nasal inflammation, olfactory epithelial metaplasia, and respiratory epithelial hyperplasia.

Table 1. Incidence of respiratory tract lesions in mice chronically exposed to naphthalene vapors.

	0 ppm	*10 ppm*	*30 ppm*
Nasal inflammation	0/69	67/69	133/135
Olfactory epithelial metaplasia	0/69	66/69	134/135
Respiratory epithelial hyperplasia	0/69	66/69	134/135

CD-1 mice were administered 5.3, 53, or 133 mg/kg /day naphthalene by gavage over 90 days (Shopp *et al.*, 1984). The only effect noted was inhibition of aryl hydrocarbon hydroxylase activity. However, the researchers did not conduct an histopathological examination.

B6C3F1 mice were administered 200 mg naphthalene/kg bw/day by gavage for 5 days per week over 13 weeks. No adverse effects were observed. (U.S. EPA, 1990).

Developmental effects of naphthalene ingestion was studied by Navarro and associates (1991). The lowest dose tested (50 mg/kg/day) was associated with adverse maternal effects. Fetal growth, survival , and morphological development were not significantly affected at 450 mg/kg/day compared with control animals, though a trend toward decreased fetal weight and increased malformations was observed.

Harris and associates (1979) administered 395 mg/kg/day naphthalene over days 1 though 15 of gestation. Fetuses had a 50% increase in incidence in delayed cranial ossification and heart development.

New Zealand white rabbits were given 0, 40, 200, or 400 mg/kg/day by gavage over days 6 through 18 of gestation (U.S. EPA, 1986a or b). A dose-dependent increase in grooming, vocalization, aggression, diarrhea, dyspnea, and ocular and nasal discharge were noted at all doses. No statistically significant increase in malformations or developmental abnormalities was observed.

Sprague-Dawley rats were administered 0, 100, 300, or 1000 mg/kg/day of naphthalene via dermal application (U.S. EPA, 1986a or b). No effects were reported at 100 or 300 mg/kg/day. At the high dose a slight decrease in testes weight was noted.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	NTP (1992)
Study population	B6C3F1 mice (75 or 150/group/sex)
Exposure method	Discontinuous whole-body inhalation exposures to 0, 10, or 30 ppm naphthalene vapor
Critical effects	Nasal inflammation, olfactory epithelial metaplasia, and respiratory epithelial hyperplasia
LOAEL	10 ppm (96% incidence for males and 100% incidence for females)
NOAEL	Not observed
Exposure continuity	6 hours/day for 5 days/week
Average experimental exposure	1.8 ppm (10 ppm x 6/24 x 5/7) for LOAEL group
Exposure duration	104 weeks
Subchronic uncertainty factor	Not required
LOAEL uncertainty factor	10
Interspecies uncertainty factor (UF)	10
Intraspecies uncertainty factor (UF)	10
Cumulative uncertainty factor	1000
Inhalation reference exposure level	0.002 ppm (2 ppb, 0.009 mg/m^3, 9 $\mu g/m^3$)

The NTP study was chosen for the REL derivation as it is the only available lifetime animal inhalation bioassay and because no adequate epidemiological studies of long-term human exposure are available. The study was judged to be of adequate study design. The complete lack of nasal effects among control animals and the nearly total effect among animals exposed at 2 different concentrations strongly indicates a causal relationship between naphthalene exposure and nasal effects. The effects seen are consistent with those reported among exposed workers, who developed rhinopharyngolaryngitis or laryngeal carcinoma (Wolf, 1976). However, the hematological effects observed in humans have not been reported in laboratory animals, which raises the possibility that humans may be significantly more sensitive to naphthalene.

The most important limitation of the study is that the lowest concentration tested caused adverse effects in most (≥96%) of the animals tested. Thus the study amply demonstrates the risk of lifetime exposures to 10 ppm, but is uninformative regarding the concentration-response relationship at lower concentrations. Only a general assumption can be drawn on the magnitude of uncertainty factor needed to predict a concentration at which adverse effects would most likely not be observed. Lacking specific guidance or relevant research for this situation, the default 10-fold factor was applied.

VII. References

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CHRONIC TOXICITY SUMMARY

NICKEL AND NICKEL COMPOUNDS

Molecular Formula	*Molecular Weight*	*Synonyms*	*CAS Registry Number*
Ni	59	elemental nickel	7440-02-0
NiO	74.69	nickel oxide	1313-99-1
$NiCl_2$	129.6	nickel chloride nickel dichloride	7718-54-9
$NiSO_4$	154.75	nickel sulfate nickelous sulfate	7786-81-4
$NiCO_3$	118.7	nickel carbonate carbonic acid nickel salt	3333-67-3
Ni_3S_2	240.19	nickel subsulfide trinickel disulfide heazlewoodite	12035-72-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.05 μg Ni/m^3**
Critical effect(s)	Lung, nasal epithelial and lymphatic pathology in male and female rats
Hazard index target(s)	Respiratory system; immune system

II. Physical and Chemical Properties (from HSDB, 1995)

Molecular formula	See above
Molecular weight	See above
Description	Ni metal: Silvery metal, $NiCl_2$: deliquescent crystals (U.S.EPA, 1985)
Specific gravity	8.9 @ 20°C (Ni)
Boiling point	2730°C (Ni)
Vapor pressure	Not applicable
Solubility	Elemental nickel, nickel subsulfide, and nickel oxide are insoluble in water, but are soluble in dilute nitric, hydrochloric, and sulfuric acids. The chloride and sulfate forms of nickel are water soluble.
Conversion factor	Not applicable for fumes and dusts

III. Major Uses and Sources

The most common airborne exposures to nickel compounds are to insoluble nickel compounds such as elemental nickel, nickel sulfide, and the nickel oxides from dusts and fumes. Contributions to nickel in the ambient air are made by combustion of fossil fuels, nickel plating and other metallurgical processes. The most common oxidation state of nickel is the divalent (Ni^{2+}) form (U.S.EPA, 1985). Elemental nickel is a malleable, silvery-white metal that is highly resistant to strong alkali. Because of its corrosion resistance, nickel is used in the production of stainless steel, permanent magnets, and other alloys that require resistance to extremes of temperature or stress (U.S.EPA, 1985). Nickel is also used in electroplating baths, batteries, textile dyes, and catalysts (U.S.EPA, 1985). Nickel dust or powder is flammable (CDTSC, 1985). Due to its unique toxicological and physico-chemical properties, nickel carbonyl is not included in this summary.

IV. Effects of Human Exposure

Several studies have indicated that occupational inhalation exposure to nickel aerosols can result in development of asthma specific to nickel. Davies (1986) found 3 cases of asthma out of 53 nickel-plating workers without a history of asthma prior to employment. Novey *et al.* (1983), described biphasic metal-specific bronchial responses in an individual metal-plating worker exposed to nickel and chromium salts. In another case, immunological studies conducted in a 24-year old man showed nickel-specific antibodies in the serum after several weeks of working in a nickel-plating shop using nickel sulfate (McConnell *et al.*, 1973). Dermatitis was observed on exposed areas of his skin, and pulmonary function, measured by FEV_1 with and without isoproterenol challenge, was significantly impaired compared with a control subject and normal values. Dyspnea, non-productive cough, chest-tightness, and wheezing were reported as symptoms by this worker during the work period.

A group of 7 metal plating workers with occupational asthma were evaluated for atopy and pulmonary function challenge in response to inhalational challenge with nickel and other metals (Cirla *et al.*, 1985). Three of the asthmatics tested positive for the presence of nickel-specific IgE antibodies. Positive reactions to skin testing with nickel were found in 3 of the asthmatic workers who also had dermatitis. Six out of the 7 asthmatics exhibited significantly decreased FEV_1 (> 15%) when exposed to 0.3 mg/m^3 nickel sulfate for 30 minutes. Control challenges with other metal salts did not reveal similar deficits in FEV_1.

Although asthma has been described in the above studies, occupational inhalation of nickel dusts has not been found to be associated with pulmonary fibrosis (Muir *et al.*, 1993). An occupational epidemiology report by Broder *et al.* (1989) found no significant effects on pulmonary function in relation to nickel exposure in a nickel smelter, however a healthy worker effect was observed in this study.

V. Effects of Animal Exposure

Early studies on the chronic non-cancer effects of metallic nickel dust were complicated by early mortality and cancer in guinea pigs and rats (Hueper, 1958).

A 2-year inhalation study of nickel oxide in rats and mice (65 per sex, per group) was conducted by the National Toxicology Program (NTP, 1994a). In the first study, rats were exposed to 0, 0.62, 1.25, or 2.5 mg nickel oxide/m^3 (0, 0.5, 1.0, or 2.0 mg Ni/m^3) 6 hours/day, 5 days/week for 104 weeks. In addition to the carcinogenic effects of nickel oxide, a number of non-cancerous lesions were observed, particularly in the lungs. The incidence of inflammatory pigmentation in the alveoli was significantly greater in all exposed groups, compared to controls. The severity of the lesions reportedly increased with increasing exposure. Atypical alveolar hyperplasia was also seen in all exposed groups. Lymphoid hyperplasia in the bronchial lymph nodes was observed in males and females exposed to 1 mg Ni/m^3 or greater at 7 and 15 months and the incidence generally increased with increasing concentration at the end of the 2-year study. Females had an increased incidence of adrenal medullary hyperplasia at all exposures of nickel oxide. Body weights were significantly lower in the groups exposed to 2.0 mg Ni/m^3 for both sexes, and in males exposed to 1.0 mg Ni/m^3.

A companion study on nickel oxide in mice conducted by NTP showed similar lung inflammatory changes as seen in the rats, in addition to pigmentation of the alveolar region at all exposure concentrations, compared with controls (NTP, 1994a). The mice were exposed to 0, 1.0, 2.0, or 3.9 mg Ni/m^3. Bronchial lymph-node hyperplasia was also evident in all nickel-exposed animals. Body weights were slightly but significantly lower in the 3.9 mg Ni/m^3 group, compared with controls.

A continuous exposure of rats (20 - 40 per group) to 0, 60, or 200 μg Ni/m^3 as nickel oxide for 2 years resulted in severe pulmonary damage and premature mortality so that carcinogenesis could not be evaluated (Glaser *et al.*, 1986). Pulmonary alveolar proteinosis and septal fibrosis were observed in the animals exposed to nickel. Only 1 rat per group survived the nickel exposures to the end of the experiment.

A 2-year study on the effects of nickel subsulfide in rats and mice was conducted by NTP (1994b). Rats (52-53 per sex per group) were exposed to 0, 0.15, or 1 mg Ni_3S_2/m^3 (0, 0.11, or 0.73 mg Ni/m^3) for 6 hours/day, 5 days/week for 104 weeks. Body weights were lowered in rats exposed to 0.73 mg Ni/m^3 compared with controls. Lung inflammation, alveolar hyperplasia, macrophage hyperplasia, and pulmonary fibrosis was observed with a significantly increased incidence at both nickel concentrations. Female rats exposed to nickel had significantly increased adrenal medullary hyperplasia. In addition to the pulmonary lesions, nasal inflammation and olfactory epithelial atrophy was observed in both sexes exposed to 0.73 mg Ni/m^3.

In the second phase of the NTP study (NTP, 1994b), mice were exposed to 0, 0.6, or 1.2 mg Ni_3S_2/m^3 (0, 0.44, or 0.88 mg Ni/m^3) for 6 hours/day, 5 days/week for 104 weeks. The same pathological lesions were observed in the lung and nasal passages as in the rats in the above

study. These lesions were evident at both the 0.44 mg Ni/m^3 and the 0.88 mg Ni/m^3 concentrations. The adrenal medullary hyperplasia seen in female rats was not observed in the mice.

An exposure of rats to either 0, or 0.97 mg Ni_3S_2/m^3 (0, or 0.71 mg Ni/m^3) for 6 hours/day, 5 days/week for 78-80 weeks resulted in decreased body weight, hyperplasia, metaplasia, and neoplasia in the lungs (Ottolenghi *et al.* (1974)).

The NTP (NTP, 1994c) studied the chronic non-cancer and carcinogenic effects of nickel sulfate hexahydrate on rats and mice. Rats were exposed to 0, 0.12, 0.25, or 0.5 mg $NiSO_4$/m^3 (0, 0.03, 0.06, or 0.11 mg Ni/m^3) for 6 hours/day, 5 days/week for 104 weeks. Chronic effects of nickel exposure in rats included inflammatory lesions in the lung, lung macrophage hyperplasia, alveolar proteinosis, and fibrosis, in addition to bronchial lymph node hyperplasia and nasal epithelial atrophy. The above effects were seen at exposures of 0.06 mg Ni/m^3 or greater.

Mice were exposed to a similar regimen that included 0, 0.06, 0.11, and 0.22 mg Ni/m^3 as nickel sulfate hexahydrate (NTP, 1994c). Similar pulmonary, lymphatic and nasal changes were observed in the mice as with the rats. Fibrosis was not reported, but an increased incidence of interstitial infiltration and alveolar proteinosis were observed at exposures of 0.11 mg Ni/m^3 or greater. No clinical findings or hematological effects were observed, but body weights were significantly depressed in all groups of nickel-exposed female mice. The body weights of males were reduced only in the group exposed to 0.22 mg Ni/m^3.

Rats and mice (10 per group) were exposed to nickel sulfate, nickel subsulfide, or nickel oxide 6 hours/day, 5 days/week, for 13 weeks (Dunnick *et al.*, 1989). Exposure-related increases in lung weight and histological lesions were observed in both species for all nickel exposures. Histological lesions included inflammatory changes, fibrosis, and alveolar macrophage hyperplasia. Nasal lesions were also observed in animals treated with nickel sulfate or nickel subsulfide. Lung weight changes were observed at exposures of 0.05 mg Ni/m^3 or greater in female rats. Macrophage hyperplasia in the alveolar region was observed at concentrations as low as 0.02 mg Ni/m^3. Additional inflammatory lesions in the lungs were observed at 0.1 mg Ni/m^3.

A similar study by Haley *et al.* (1990) found that exposure of mice to nickel sulfate, nickel subsulfide, or nickel oxide resulted in various immunological effects. Mice were exposed to 0, 0.11, 0.45, or 1.8 mg Ni/m^3 as Ni_3S_2; 0.47, 2.0, or 7.9 mg Ni/m^3 as NiO; and 0.027, 0.11, and 0.45 mg Ni/m^3 as $NiSO_4$ for 6 hours/day, 5 days/week for 13 weeks. Nickel exposures consistently decreased splenic antibody-forming cell (AFC) responses, with significant decreases occurring at 1.8 mg Ni/m^3 as nickel subsulfide. In contrast, AFC responses in the lung-associated lymph nodes were consistently increased, indicating a possible indirect influence of inflammatory mediators released in the lung on local lymph nodes.

Rabbits (8 nickel exposed and 8 controls) exposed to 0.24 mg Ni/m^3 as nickel chloride 6 hours/day, 5 days/week for 4 weeks exhibited significantly decreased macrophage lysozyme activity in pulmonary lavage fluid and in macrophage cultures, compared with control animals

(Lundborg and Camner, 1984). Similar exposures of rabbits to chlorides of cadmium, cobalt, or copper did not reduce lysozyme activity.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	National Toxicology Program, 1994c
Study population	Male and female F344/N rats (52-53 per group)
Exposure method	Discontinuous inhalation
Critical effects	Pathological changes in lung, lymph nodes, and nasal epithelium: (1) active pulmonary inflammation (2) macrophage hyperplasia (3) alveolar proteinosis (4) fibrosis (5) lymph node hyperplasia (6) olfactory epithelial atrophy
LOAEL	60 μg Ni/m^3 (as nickel sulfate hexahydrate)
NOAEL	30 μg Ni/m^3
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	104 weeks
Average experimental exposure	5.4 μg Ni/m^3 for NOAEL group
Human equivalent concentration	1.6 μg Ni/m^3 for NOAEL group males (particulate with respiratory effects, RDDR = 0.29 based on MMAD = 2.5, sigma g = 1.26, male rat body weight = 380 g, SA(PU) = 0.34 m^2, DEP(PU) = 0.024)
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.05 μg Ni/m^3

The studies conducted by NTP (1994 a,b, & c) all showed similar non-carcinogenic effects in rats and mice, regardless of the form of nickel administered. It therefore appears that soluble and insoluble forms of nickel cause similar effects in rodents. The human epidemiological literature predominantly describes cancer mortality rates from occupational exposures to nickel compounds, but does not specifically examine non-cancer effects. However, it is clear from many case reports that allergies and dermatitis can occur in exposed workers. Hypersensitive reactions to nickel have not been quantitatively studied in humans or animals, therefore it is not possible to develop an REL based on immunological hypersensitivity at the present time. A host of subacute and subchronic animal studies have shown nickel to affect certain immunological responses unrelated to hypersensitivity, but the applicability of these results to chronic human

exposures and responses involves considerable uncertainty. Furthermore, data show that nickel may precipitate onset of asthma in occupational settings.

The strengths of the inhalation REL include the availability of controlled lifetime exposure inhalation studies in multiple species at multiple exposure concentrations and with adequate histopathogical analysis and the observation of a NOAEL. The major areas of uncertainty are the lack of adequate human exposure data and the lack of lifetime toxicity studies in any non-rodent species.

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CHRONIC TOXICITY SUMMARY

NITRIC ACID

(Aqua fortsi; hydrogen nitrate; red and white fuming nitric acid)

CAS Registry Number: 7697-37-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**40 μg/m^3**
Critical effect(s)	Pulmonary edema, emphysema, inflammation in rats
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties (HSDB, 1995; ATSDR, 1989)

Molecular formula	HNO_3
Molecular weight	63.02 g/mol
Description	Fuming colorless or yellowish liquid with a characteristic choking odor
Vapor pressure	0.3513 torr @ 25° C
Solubility	Soluble in all proportions in water, soluble in ether
Conversion factor	1 ppm = 2.58 mg/m^3 at 25´C

III. Major Uses or Sources (HSDB, 1995)

Nitric acid (HNO_3) is the most common strong acid which is also a strong oxidizing agent. It is used to dissolve noble metals, and in the etching and cleaning of metals. It is also used to make nitrates and nitrocompounds, especially organic compounds, many of which are commercial or military explosives. HNO_3 is also used to destroy residues of organic matter. The primary use of nitric acid is the production of ammonium nitrate fertilizer. Decomposition of HNO_3 releases nitrogen dioxide (NO_2) and nitric oxide (NO). In practice, HNO_3 is usually found in conjunction with NO_2 which appears to be more hazardous (ACGIH, 1991). HNO_3 is also present in indoor and outdoor air pollution.

IV. Effects of Human Exposure

Fairhall (1957) noted that continued exposure to nitric acid vapor and mist may result in chronic bronchitis. More severe exposures may cause chemical pneumonitis. No exposure duration or concentrations were provided.

NIOSH (1976) indicated that prolonged exposures at high concentrations to nitric acid mists or vapors may cause erosion of exposed teeth.

Ostro *et al.* (1991) studied a panel of 207 male and female asthmatics residing in the Denver area for several months in the winter. Daily concentrations of nitric acid, sulfates, fine particulates, and hydrogen ion were measured. A multiple regression time-series model was used to measure associations of pollutant exposure and self reported daily health outcomes, respiratory symptoms, and medication use by study participants. Investigators found that nitric acid and nitrates were not significantly associated with any respiratory symptom analyzed. Although personal exposure measurements were crude and symptoms were self-reported, a NOAEL up to 13.54 $\mu g/m^3$ (5.25 ppb) (range: 0.06 - 13.54, mean 1.81 $\mu g/m^3$) was found in this sensitive population.

V. Effects of Animal Exposure

Gray *et al.*, (1952) exposed four groups of 10 rats for 4 hours/day, 5 days/week to red fuming nitric acid for 40-96 hours for a period of 10-24 days. The concentration was given as 9 to 14 ppm (23.2 - 36.1 mg/m^3) NO_2. In general, 14% of red fuming nitric acid is in the form of NO_2 (ACGIH, 1991) and 86% is generally in the form of HNO_3. Therefore, animals were exposed to approximately 64 - 100 ppm HNO_3 (160 - 250 mg/m^3). Animals examined shortly after exposure exhibited an inflammatory condition throughout the entire respiratory tract, with the upper respiratory tract being more severely affected. Rhinitis, tracheitis, and pneumonitis were also seen. Animals examined eight or more weeks after exposure exhibited less inflammation; however, localized areas of emphysema were seen in all lobes of the lung. Gray *et al.* (1954) later conducted a chronic exposure study on 90 rats, 30 mice, and 10 guinea pigs exposed to a nitric acid concentration of 4 ppm (10.3 mg/m^3) for 4 hours/day, 5 days/week for a duration of 6 months. Results indicated no significant pathologic changes among treated animals compared to controls.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Gray *et al.* (1952; 1954)
Study population	Mice, rats, guinea pigs
Exposure method	Discontinuous inhalation (0 and 9 to 14 ppm in Gray, 1952); 0 and 4 ppm in Gray, 1954)
Critical effects	Pulmonary changes, inflammation, emphysema
LOAEL	Mean of 11.5 ppm (9 to 14 ppm) (Gray, 1952)
NOAEL	4 ppm (Gray, 1954)
Exposure continuity	4 hours/day, 5 days/week (Gray, 1952; 1954)
Exposure duration	10 to 24 days (Gray, 1952) 6 months (Gray, 1954)
Average exposure concentration	0.48 ppm for NOAEL group
Human equivalent concentration	0.41 ppm for NOAEL group (gas with pulmonary effects, guinea pig RGDR = 0.86, based on BW = 435 g, MV = 0.20, SA(PU) = 9,000 cm^2)
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.014 ppm (0.036 mg/m^3; 40 $\mu g/m^3$)

The Gray *et al.* (1954) study was selected since it was the only study which demostrates a NOAEL in animals chronically exposed to HNO_3. Although the results indicate that animals exposed to 4 ppm (10 mg/m^3) red fuming HNO_3 showed no significant pathologic changes when compared to control animals, few details are given as to the types of changes the researchers were looking for. In an earlier study, Gray *et al.* (1952) exposed four groups of 10 rats to 64 - 100 ppm (160 - 250 mg/m^3) red fuming nitric acid 4 hours/day, 5 days/week or a total of 40 - 96 hours over 10 - 24 days. Even animals in the lowest exposure group (4 hours/day for 10 days; mean concentration 66 ppm: range 45 - 91 ppm) exhibited inflammation throughout the entire respiratory tract, rhinitis, tracheitis, and pneumonitis. Animals examined eight or more weeks after exposure exhibited pulmonary effects such as pneumonitis and emphysema in all lobes of the lung.

An epidemiological study of confirmed asthmatics by Ostro *et al.* (1991) demonstrated a similar NOAEL to that calculated from the Gray studies. A free-standing NOAEL up to 13.54 $\mu g/m^3$ (5.25 ppb) (range: 0.06-13.54, mean 1.81 $\mu g/m^3$) was found in this sensitive subpopulation. The free-standing NOAEL does not allow for evaluation of the dose-response relationship. In comparison, the 2 studies by Gray *et al.* (1952; 1959) collectively indicate both a LOAEL and NOAEL in the same species. Although epidemiological methods in the Ostro *et al.* (1991) study are appropriate, this study was not used in the derivation of the chronic REL because exposure

methods were somewhat crude and the results represent a free-standing NOAEL. There are several factors that lend strength to the Ostro *et al.* study. Although exposure duration was only six months, all participants were residents of the Denver area and had been chronically exposed to the HNO_3 levels reported. The large number of observations in this study provided increased the degrees of freedom and stability of estimates. While problems of confounding and exposure assessment exist, they were decreased by each individual serving as his or her own control over time. Moreover, this study detected a relationship between airborne H+ and fine particulates and the self reported indicators of asthma status.

The strengths of the inhalation REL include the availability of subchronic inhalation exposure data, and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data and the lack of reproductive and developmental toxicity studies.

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CHRONIC TOXICITY SUMMARY

NITROBENZENE

(nitrobenzol; NB; oil of mirbane; essence of mirbane; NCI-C60082)

CAS Registry Number: 98-95-3

I. Chronic Toxicity Summary

Inhalation reference exposure level	**30 µg/m^3**
Critical effect(s)	Hepatie lesions in rats.
Hazard index target(s)	Alimentary system, blood system, reproductive system, respiratory system.

II. Physical and Chemical Properties

Molecular formula	$C_6H_{12}O$
Color/form	Greenish yellow crystals or yellow oily liquid (HSDB, 1996)
Molecular weight	123.11 (HSDB, 1996)
Specific gravity	1.204 at 20ºC (HSDB, 1996)
Boiling point	211ºC (HSDB, 1996)
Melting point	6ºC (HSDB, 1996)
Vapor pressure	1 mm Hg at 44.4ºC (HSDB, 1996)
Solubility	Soluble in 500 parts water; freely soluble in ethanol, benzene, ether, and oils (HSDB, 1996)
Conversion factor	5.0 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Nitrobnzene has primarily been used in the manufacture of aniline (97% of consumption) (ATSDR, 1990). It has been used in the synthesis of other chemicals. It has been used as a solvent for cellulose ethers and for modifying esterification of cellulose acetate. Nitrobezene has been used in metal polishes, soaps, spray paints, floor polishes and shoe polishes. It has also been used in the manufacture of perfumes. A total of 930 million pounds were used in the United States in 1987 (HSDB, 1996). Inhalation represents a major route of exposure to nitrobenzene (Dorigan and Hushon, 1976).

IV. Effects of Human Exposure

The adverse effect most frequently associated with human exposure to nitrobenzene has been methemoglobinemia (Beauchamp *et al.*, 1982). Occupational poisoning by nitrobenzene has occurred, leading to hemolytic anemia (HSDB,1996). Cyanosis, ephoria, facial flushing, and headache are commonly noted. An higher concentrations, effects noted include weakness, ataxia, and lightheadness.

Ikeda and Kita (1964) presented the case report of a person occupationally exposed to nitrobenzene for 17 months who developed headache, nausea, vertigo, confusion and paresthesia.

Infants have been severely affected by topical application of a bitter almond oil substitute containing 2 to10% nitrobenzene (Browning, 1965). Effects noted were shock, CNS depression, cold extremities and rapid pulse. Two fatal cases involved the development of bronchopneumonia.

V. Effects of Animal Exposure

The adverse effect most frequently associated with exposure to nitrobenzene has been methemoglobinemia (Beauchamp *et al.*, 1982). Histopathology has been noted in the hemato-lymphoreticular system, central nervous system, liver, adrenals, and testes. Metabolism of nitrobenzene involves either oxidation or reduction yielding p-aminophenol and p-nitrophenol, and other reduced intermediates.

Mice and rats were chronically exposed via inhalation to nitrobenzene (CIIT, 1993; Cattley *et al.*, 1994). Male and female B6C3F1 mice were exposed to 0, 5, 25, or 50 ppm for 6 hours per day, 5 days per week over 2 years. Male and female F344 rats and male CD rats were exposed to 0, 1, 5, or 25 ppm using the same exposure regimen. Slight exposure-related decreases in body weights (< 10% of control) were sometimes observed. Degenerative changes in the nose, liver, and testis; methemoglobinemia; and anemia were reported.

Female CD rats (26/group) inhaled nitrobenzene (0, 1, 10 or 40 ppm) for 6 hrs/day on gestation days 6-15 (Bushy Run Research Center, 1984). Significant effects noted in treated relative to control animals were decreased maternal body weight gain; increased spleen weight; increases in litters with fetuses with variations or ecchymoses on the trunk, parietal skull plate holes.

Groups of 12 pregnant New Zealand white female rabbits inhaled 0, 10, 40 or 80 ppm nitrobenzene for 6 hrs/day on days 13-19 of gestation (Biodynamics, 1983). Yellowish staining of fur in the ano-genital area, soft stool, and alopecia were noted. Methemoglobin levels in the 80 ppm exposure group were significantly higher than controls on day 19.

Some additional effects were noted in a followup study. Female New Zealand White rabbits (22/group) were administered nitrobenzene by inhalation (0, 10, 40 or 100 ppm) for 6 hrs/day

during gestation days 7-19 (Biodynamics, 1984). Increased absolute and relative liver weight and methemoglobin levels were reported.

Sprague-Dawley rats and B6C3F1 mice administered 125 ppm nitrobenzene for two weeks developed cerebellar damage including perivascular hemorrhage (Medinsky and Irons, 1985). Fischer rats exposed to the same concentration did not develop cerebellar lesions. Sprague-Dawley rats inhaling 35 ppm nitrobenzene for two weeks developed hepatocyte necrosis.

Male B6C3F1 mice exposed to 16 ppm nitrobenzene via inhalation for 90 days developed increased liver weight, hyperplasia, and multinucleated hepatocytes (Hamm, 1984).

Male and female Sprague Dawley CD rats (30/sex/group) inhaled nitrobenzene at concentrations of 0, 1, 10 or 40 ppm for 6 hrs/day, 5 days/week, over ten weeks (Bushyrun, 1985). Exposures were 7 days/week during a two-week mating period, a 19-day gestation period (females only), and a 17-day postpartum period (dams only). F1 generation rats (5-7 weeks of age, 30/sex/group) were exposed in the same way as the parental generation. F2 generation rats were not exposed. Among F0 animals decreased relative and absolute testes and epididymides weights and increased atrophy of the testes and epididymides were reported. Among F1 animals decreased body weights and testes size, as well as atrophy of the testes and epididymides. All nitrobenzene exposed groups had a decreased fertility index and number of dropped vaginal plugs.

Pregnant Sprague-Dawley CD rats inhaled nitrobenzene vapor (0, 1.1, 9.8, or 39.4 ppm) for 6 hours per day on gestational days 6 through 15 (Tyr *et al.*, 1987). There were no treatment-related effects on the incidence of fetal malformations or variations at gestation day 21. Maternal toxicity included reduced weight gain at 40 ppm and absolute and relative spleen weights increases at 10 and 40 ppm.).

A two-generation reproduction study was conducted with Sprague-Dawley CD rats exposed to 0, 1, 10, or 40 ppm nitrobenzene (Dodd *et al.*, 1987). No exposure-related reproductive effects were reported at 1 or 10 ppm. At 40 ppm, decreased fertility index, decreased testes weights, seminiferous tubule atrophy, and spermatocyte degeneration were noted. Litters derived from rats exposed to 40 ppm had a decreased mean body weight on postnatal day 21.

Oral exposures have also caused adverse effects. Male rats given a single oral dose (50 to 450 mg/kg) developed hepatic centrolobular necrosis and necrosis of the primary and secondary spermatocytes with multinucleated giant cells (Bond *et al.*, 1981). Male F344 rats receiving a higher single oral dose (550 mg/kg bw) developed petechial hemorrhages in the brain stem and cerebellum within 32 days of administration. Only a small fraction of the dose passed the blood brain barrier (Morgan *et al.*, 1985).

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	CIIT (1993); Cattley *et al.* (1994)
Study population	Male and female F344 rats (70/group)
Exposure method	Discontinuous inhalation exposures to 0, 1, 5, or 25 ppm nitrobenzene
LOAEL	5 ppm
Critical effects	Pigment deposition in olfactory epithelia
NOAEL	1 ppm
Exposure continuity	6 hr/day for 5 days/week
Average experimental exposure	0.18 ppm (1 ppm x 6/24 x 5/7) for NOAEL group
Exposure duration	2 years
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.006 ppm (6 ppb, 0.03 mg/m^3, 30 $\mu g/m^3$)

Increased nasal subepithelial macrophage associated pigment deposition observed at 1 ppm was of uncertain significance and therefore 1 ppm was considered as a NOAEL rather than a LOAEL.

The chronic REL is strengthened because: (1) the key study evaluated lifetime exposures, and 2) three strains of rats and mice were studied over their lifetimes.

Areas of uncertainty include: (1) the need to estimate human effects from animal data, (2) lack of continuous exposure, and (3) the lack of an observed no effect concentration.

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CHRONIC TOXICITY SUMMARY

NITROGEN DIOXIDE

CAS Registry Number: 10102-44-0

I. Chronic Toxicity Summary

Inhalation reference exposure level	**20 μg/m^3**
Critical effect(s)	Increased incidence of asthma in children
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (HSDB, 1995)

Molecular formula	NO_2
Molecular weight	46.01 g/mol
Description	Colorless liquid; reddish-brown gas
Vapor pressure	720 mm Hg @ 20° C
Solubility	Soluble in concentrated nitric and sulfuric acids; decomposes in water, forming nitric oxide and nitric acid
Conversion factor	1.88 mg/m^3 = 1ppm @ 25° C

III. Major Uses or Sources

High concentrations of nitrogen dioxide (NO_2) are found in silos where silage is stored. Varying amounts of NO_2 result from the detonation of nitro or nitrate explosives. Nitrogen dioxide is used as a nitrating agent, as a component of rocket fuels, and as an intermediate in the formation of nitric acid (HNO_3). The majority of occupational exposures result from its presence as a by-product of nitrate decomposition, as in the reaction of HNO_3 with metals or other reducing agents, various processes in which air is heated to high temperature with the formation of nitric oxide (NO), or in the exhaust of internal-combustion engines.

Major indoor sources include unvented gas stoves, other gas appliances, kerosene heaters, and indoor ice-skating rinks.

The major sources of nitrogen dioxide emissions in California are: on-road vehicles (approximately 51%), other vehicles, locomotives, aircraft (23%), and stationary combustion sources (e.g., oil and gas production, and refining, manufacturing/industrial, and electric utilities - 26%).

IV. Effects of Human Exposure

The respiratory system is the primary target of NO_2 exposure in humans. Three types of human responses have been demonstrated: i) increased sensitivity to bronchoconstrictors ii) increased airway resistance iii) enhanced susceptibility to respiratory infections. Children, asthmatics, and people with chronic obstructive pulmonary disease (COPD) are especially sensitive to the effects of NO_2 in outdoor and indoor air (Amdur 1986; Morrow and Utell, 1989; Samet *et al.*, 1993). Early community-based epidemiologic studies of outdoor air found significant associations between higher NO_2 concentrations and both lung function in school children and respiratory disease among families (Shy *et al.*, 1 970 a,b). These studies did not contain sufficient exposure measurements to allow for quantitative dose-response assessments. In addition, increased incidence of bronchitis was reported by parents of children living in neighborhoods with slightly elevated NO_2 levels (Pearlman *et al.*, 1971). A correlation between ambient NO_2 concentration and changes in lung function in children (maximal expiratory flow rate and specific airway conductance) has also been reported (Kagawa and Toyasma, 1975). Schwartz and Zeger (1990) studied the effects of air pollution among a population of nurses in Los Angeles and found a significant association between NO_2 levels and production of phlegm. Hourly concentrations of NO_2 averaged approximately 0.13 ppm (0.24 mg/m^3).

An epidemiological study in which personal NO_2 badges were used to assess household NO_2 exposure of a subset of children (Infante-Rivard, 1993) found a dose-response relationship between NO_2 (ppb) and asthma incidence. NO_2 was significantly associated with asthma at levels >15 ppb (28.2 μg/m^3). Equivocal results have been obtained in cross-sectional surveys of the effects of indoor air pollution on respiratory illness in children and adults. However, NO_2 concentrations were not quantitatively measured but inferred in many studies based on the presence or absence of a gas stove or other NO_2 emitting appliances. Some studies have found a significant association between the presence of NO_2 emitting appliances in the home and the likelihood of frequent respiratory illness or decreased pulmonary function in children living in those houses (Melia *et al.*, 1977, 1979; Neas *et al.*, 1991; Hasselblad *et al.*, 1992). Other studies have not found any relationship between respiratory effects in gas stove versus electric stove homes (Samet *et al.*, 1993; Melia *et al.*, 1982; Ware *et al.*, 1984; Dijkstra *et al.*, 1990).

V. Effects of Animal Exposure

The principle target organ of NO_2 toxicity in experimental animals is the lung. A number of laboratory studies have found effects on the respiratory system at NO_2 concentrations similar to those inhaled by urban populations (CARB, 1992). Pulmonary and extrapulmonary effects observed due to chronic exposure in experimental animals include: increased susceptibility to respiratory infection, deterioration of respiratory defense mechanisms, irreversible structural damage to the lung, and immunological alterations.

Increased susceptibility to infection and subsequent mortality from streptococcal infection was seen in mice exposed to 0.2 ppm (0.4 mg/m^3) NO_2 5 day/week for 1 year plus two 0.8 ppm (1.5 mg/m^3) spikes/day of 1 hour each (Miller *et al.*, 1987). Ehrlich and Henry (1968)

demonstrated increased mortality from *K. pneumoniae* infection after 6-month intermittent bacterial challenge and continuous exposure to 0.5 ppm (0.9 mg/m^3) NO_2. A study of shorter duration found that continuous exposure of mice to 0.5 ppm (0.9mg/m^3) for three months had no effect on mortality from *K. pneumoniae* infection (McGrath and Oyervides, 1985).

Adverse effects on lung morphology including pulmonary edema, emphysema, and thickened bronchial epithelium have been reported after chronic and subchronic exposure to low levels of NO_2. Rats exposed continuously to 0.4 ppm (0.75 mg/m^3) NO_2 exhibit increased pulmonary lipid peroxidation after 18 months (Sagai *et al.*, 1984). Replacement of injured Type I cells lining the alveoli by Type II cells was seen in mice exposed to 0.34 ppm (0.64 mg/m^3) NO_2 for 5 days/week over a six week period (Sherwin and Richters, 1982). Rats continuously exposed to 0.11 ppm (0.21 mg/m^3) and 0.46 ppm (0.86 mg/m^3) NO_2 for 1 month also demonstrated an increase in air-blood barrier thickness (Kyono and Kawai, 1982). Ferrets exposed to low (0.5 ppm) and high (10 ppm) concentrations of NO_2 for 4 hours/day, 5 day/week, at ages 6-20 weeks also showed thickened alveolar walls and signs of oxidant damage at both levels (Rasmussen and McClure, 1992). Data from chronic studies are equivocal and it has been suggested that morphological effects may or may not be evident depending upon the use of light or electron microscopy for assessment of injury (CARB, 1992). No changes occurred in rats exposed to 1.0 ppm (1.88 mg/m^3) for 15 weeks (Gregory *et al.*, 1983) or in squirrel monkeys exposed to 1.0 ppm (1.88 mg/m^3) NO_2 for 16 months (Fenters *et al.*, 1973). No changes were seen in guinea pigs, rabbits, dogs, monkeys, and rats exposed to 0.53 ppm (1.0 mg/m^3) NO_2 continuously for 90 days (Steadman *et al.*, 1966).

Rats exposed for 27 months developed a significant increased thickening of the air-blood barrier at 0.4 ppm (0.7 mg/m^3) but not at 0.04 ppm (0.07 mg/m^3) (Kubota *et al.*, 1987). Type II cell hypertrophy and interstitial edema occurred in rats exposed continuously to 0.5 ppm (0.9 mg/m^3) NO_2 for 4 months, increased thickness of alveolar septa by 6 months, and fibrous pleural thickening by 19 months (Hayashi *et al.*, 1987). Dogs exposed to 1.0 ppm (1.88 mg/m^3) NO_2 6 hours/day, 5 days/week developed dialated alveoli and ducts at 12 months exposure. Edema, thickened alveolar septa, and inflammation occurred after 18 months (Wagner *et al.*, 1963).

Low level NO_2 exposure has also been shown to cause cellular damage and structural lung changes leading to the development of emphysema. Hamsters exposed to 2 ppm (3.8 mg/m^3) NO_2 for 8 hour/day, 5 day/week for 8 weeks showed mild emphysematous lesions (Lafuma *et al.*, 1987). Beagle dogs exposed to 0.6 ppm (1.1 mg/m^3) NO_2 and 0.16 ppm NO_2 16 hour/day for 68 months developed emphysema. Dogs exposed to 0.14 ppm NO_2 (0.26 mg/m^3) and 0.11 ppm NO did not, indicating NO_2 was likely the inducing agent (Hyde *et al.*, 1978).

VI. Derivation of Chronic Reference Exposure Level (RfC)

Study	Infante-Rivard (1993)
Study population	Asthmatic children
Exposure method	Continuous inhalation of indoor air
Critical effects	Incidence of asthma
LOAEL	15 ppb (30 µg/m^3)
NOAEL	Mean of 12.5 ppb (range 10-15 ppb)
Exposure continuity	Continuous exposure
Exposure duration	Potential lifetime exposure
Average exposure concentration	12.5 ppb for NOAEL group
Human equivalent concentration	12.5 ppb for NOAEL group
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	1
Cumulative uncertainty factor	1
Inhalation reference exposure level	0.01 ppm (10 ppb; 0.02 mg/m^3; 20 µg/m^3)

This well-designed epidemiologic study was chosen because it is one of the only studies which utilized personal monitors to assess indoor as well as outdoor exposure to NO_2. This is an important factor since most people generally spend 75-90 percent of their time indoors. Previous studies of indoor NO_2 exposure relied upon the existence of certain appliances in the home to assess exposure and previous ecological studies relied upon regional measurements to assess personal exposure. Therefore in both types of studies misclassification bias was a factor. The investigator of this study also used asthma incidence instead of prevalence as a critical effect to reduce survival and migration biases.

In this study a dose-response relationship between NO_2 and asthma was seen. The odds ratio for children with exposure at 15 ppb compared with those below 15 ppb or less was 9.66 (95% CI 3.64-25.58). With adjustment for allergy, eczema, parental asthma, pneumonia, tonsillectomy, absence of breastfeeding, mothers smoking, and presence of other smokers in the home, the odds ratio was 10.61 (95% CI 3.62-30.69). The author also attempted to assess the interaction between NO_2 exposures and markers of sensitization. Although the sample size was somewhat small for this type of analysis, odds ratios were 6.60 when no animals were present and 25.2 in households with animals (Infante-Rivard, 1995).

Other epidemiological studies have found respiratory effects at somewhat higher levels. Neas and colleagues (1991) have reported odds ratios of 1.45 for lower respiratory symptoms in children associated with an increase in annual average nitrogen dioxide concentration of 15 ppb. A recent meta analysis of 11 epidemiological studies suggested a 20% increase in the odds ratio for lower respiratory infection for children associated with a prolonged increase to 16 ppb nitrogen dioxide (Hasselblad *et al.*, 1992). Moseler *et al.*, (1994) reported children with

asthmatic symptoms were susceptible to having reduced lung function when exposed to outdoor air pollution where average NO_2 concentrations exceed 21 ppb (40 $\mu g/m^3$).

Acute controlled exposure studies have found effects in asthmatics at NO_2 levels 10-15-fold higher than the chronic REL. To determine if NO_2 exposure influenced sensitization, Tunnicliffe *et al.* (1994) exposed ten asthmatics to 100 and 400 ppb $N0_2$ for 1 hour before undergoing house mite allergen challenge. The difference in FEV_1 for early and late asthmatic challenges were significantly different between air and 400 ppb NO_2 suggesting that exposure to concentrations encountered in the home could potentiate specific airway responses. Significant differences between air controls and the 100 ppb group were not seen. Increased airway reactivity has been observed after acute exposures to NO_2 ranging from 100-500 ppb for 20 minutes-4 hours duration in six studies of asthmatics (Orehek *et al.* 1976; Kleinman *et al.* 1983; Jorres *et al.* 1990; Bauer *et al.* 1986; Bylin *et al.* 1985; Mohsenin, 1987) and in one study of individuals with chronic obstructive pulmonary disease (COPD) (Morrow *et al.*, 1992). It is possible that the incidence of increased airway reactivity would be similar whether exposures were chronic or acute and that these values could also be interpreted as LOAELS for chronic NO_2 exposure. However it should be noted that exposure affecting airway reactivity could increase morbidity from existing asthma as well as decrease the threshold of allergen exposure needed to develop sensitization and allergic asthma. Other subchronic and chronic animal studies have shown increased susceptibility to infection, increased air blood barrier thickness, and oxidant damage at these same levels (100-500 ppb (188-940 mg/m^3)-see text). Low level NO_2 exposure has also been shown to cause cellular damage and structural changes leading to the development of emphysema in dogs and hamsters however a quantitative extrapolation from experimental animals to humans has not been made (Hayashi *et al.*, 1987; Wagner *et al.*, 1965).

The strengths of the inhalation REL include the use of human exposure data from a sensitive subpopulation and the observation of a NOAEL. The major area of uncertainty is the lack of reproductive and developmental toxicity studies.

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CHRONIC TOXICITY SUMMARY

2-NITROPROPANE

(2-NP; β-nitropropane; dimethylnitromethane; isonitropropane; nitroisopropane; NIPAR S-20 Solvent; NIPAR S-30 Solvent)

CAS Registry Number: 79-46-9

I. Chronic Toxicity Summary

Inhalation reference exposure level	**20 µg/m^3** (U.S. EPA RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC
Critical effect(s)	Liver effects (increased liver weight; focal hepatocyte vacuolization and nodules) in rats
Hazard index target(s)	Alimentary system

II. Physical and Chemical Properties (HSDB, 1994)

Description	Colorless liquid
Molecular formula	$C_3H_7NO_2$
Molecular weight	89.09 g/mol
Specific gravity	3.06 @ 25 ^oC(air = 1)
Boiling point	120.3 ^oC
Melting point	-93 ^oC
Vapor pressure	20 mm Hg @ 25 ^oC
Solubility	Soluble in chloroform
Conversion factor	1 ppm = 3.64 mg/m^3 at 25° C

III. Major Uses or Sources

The nitroalkane, 2-nitropropane, acts as a common component (5 to 25%) in a variety of industrial solvent systems in order to improve drying time; to insure more complete solvent release; to provide better flow characteristics and film integrity; to increase wetting ability and electrostatic spraying properties; or to insure greater pigment dispersion. Several industrial coatings utilize 2-nitropropane including vinyl, epoxy, nitrocellulose and chlorinated rubbers. Propellants, such as gasoline, diesel, and rocket fuels, use 2-nitropropane as an additive. Paint and varnish removers, printing inks, adhesives, and explosives may also contain 2-nitropropane (HSDB, 1994).

IV. Effects of Human Exposures

Minimal human toxicity data exists for 2-nitropropane. As reported by the U.S. EPA (1994) no occupational epidemiological studies are available; and case reports on only 7 acutely exposed workers (6 fatalities) have been described (Rondia, 1979; Hine *et al.*, 1978; Harrison *et al.*,1985). All of these studies reported evidence of liver damage.

V. Effects of Animal Exposures

A series of 2-nitropropane inhalation studies conducted with Sprague-Dawley rats found adverse effects in the liver (Angus Chemical Co., 1985 a,b; Griffin *et al.*, 1980, 1981). These four studies report the toxicity results from four concentrations of 2-NP exposure, 0, 25, 100 and 200 ppm (0, 78, 312, or 624 mg/m^3, respectively as based on authors' chamber temperature and atmospheric conditions at 25^{o}C 1350 m altitude, conversion factor of 1 ppm = 3.12 mg/m^3). Griffin *et al.* (1980, 1981) report results from the lowest concentration studied (25 ppm), while the Angus Chemical Co. (1985a,b) report results from the same investigators done at 100 and 200 ppm exposures. Sprague-Dawley rats (125/sex/group) received 0 or 25 ppm (0 or 78 mg/m^3) 2-nitropropane 7 hours/day, 5 days/week for 22 months (Griffin *et al.*, 1980; 1981). Interim sacrifices (10/animals/group) were conducted at 1, 3, 6, and 12 months, while recovery groups were exposed for 3 or 12 months and maintained without exposure for 19 and 10 months respectively. Hematologic parameters, organ weights, serum clinical chemistry and complete histopathology were conducted. Adverse treatment related changes were reported in the liver as an increase in focal vacuolization of the hepatocytic cytoplasm (males only), slight hepatic congestion, and focal areas of hepatocellular nodules (Griffin *et al.*,1980). No exposure-related effect on any other tissue was reported (Griffin *et al.*,1981). A LOAEL of 25 ppm (78 mg/m^3) 2-nitropropane for these mild hepatic effects was determined.

Similar adverse hepatic effects of 2-nitropropane exposure were observed in related studies exposing rats (125/sex/group) to 100 ppm (Angus Chemical Co.,1985a) and 200 ppm (Angus Chemical Co.,1985b) 2-nitropropane 7 hours/day, 5 days/week for either 18 (100 ppm group) or 6 months (200 ppm group). At 100 ppm (312 mg/m^3), exposed male rats had increased liver weight and decrease body weight versus controls. Increased SGPT levels (4.6 fold increase over controls) were also observed in males. No histopathological examination of liver or lungs was performed (Angus Chemical Co.,1985a). The study exposing Sprague-Dawley rats to 200 ppm (624 mg/m^3) 2-nitropropane included complete histological examination and interim sacrifices (10/group) at 10 days, 1 months and 3 months. Increased SGPT (4.5 fold over controls) was observed at 6 months in male rats. A significant elevation in relative liver weights occurred at 3 and 6 months for both sexes. Liver histological changes became apparent as vacuolization and necrosis at 10 days and 1 month. At 3 and 6 months exposure hepatic cytoplasmic vacuolization, nuclear change, and cell necrosis increased in male rats. Hypertrophic areas and nodules were seen in males by 6 months exposure. Heptacellular changes in females were milder than in males, consisting of slight vacuolization at 6 months. This study confirmed the higher susceptibility of male versus female rats to the hepatic effects of 2-nitropropane exposure.

In a 6-month inhalation study, male Sprague-Dawley rats (50 animals/group) and 15 male New Zealand rabbits (15/group) were exposed to 0, 27, or 207 ppm (0, 98.3, or 753 mg/m^3) 2-nitropropane 7 hours/day, 5 days/week (Lewis *et al.*, 1979). Interim sacrifices were conducted at 2 and 10 days, 1, 3, and 6 months for rats (10/group), and at 1, 3, and 6 months for rabbits (5/group). No treatment related effects were observed at the low (27 ppm) concentration in rats, or at either concentration in rabbits. Rats exposed to 207 ppm demonstrated increased liver and lung weights, and an increased incidence of focal necrosis, hypertrophic nodules, and altered liver appearance, at 3 months versus controls. Additionally the lungs of these rats exposed to the highest concentration had a higher incidence of hemorrhagic foci and pulmonary edema after 1 month relative to controls. Multiple hepatocellular carcinomas were present in the livers of all rats in the high-concentration group sacrificed at 6 months post-exposure.

No reproductive or developmental studies for inhalation or oral exposure to 2-nitropropane in animals have been reported. One study reported fetal toxicity, without maternal toxicity, due to delayed fetal development following i.p. injection of 170 mg/kg in Sprague-Dawley rats on days 1-15 of gestation (Hardin *et al.*,1981).

VI. Derivation of U.S. EPA RfC

Study	Griffin *et al.* (1980, 1981)
Study population	Sprague-Dawley rats
Exposure method	Discontinuous whole-body inhalation exposures (0 or 25 ppm)
Critical effects	Liver focal vacuolization and nodules
LOAEL	25 ppm
NOAEL	Not observed
Exposure continuity	7 hours/day, 5 day/week
Exposure duration	22 months
Average experimental exposure	5.2 ppm for NOAEL group
Human equivalent concentration	5.2 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
LOAEL uncertainty factor	3
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Modifying factor	10
Cumulative uncertainty factor	1,000
Iinhalation reference exposure level	0.005 ppm (5 ppb, 0.02 mg/m^3, 20 µg/m^3)

The strengths of the inhalation REL include the availability of chronic inhalation exposure data from a well-conducted study with histopathological analysis. Major areas of uncertainty are the lack of adequate human exposure data, the lack of observation of a NOAEL, and the lack of reproductive and developmental toxicity studies.

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CHRONIC TOXICITY SUMMARY

PENTACHLOROPHENOL

(PCP, penchlorol, chlorophen, penta, Pentachlorphenol (German), pentachlorofenol, pentachlorofenolo, 2,3,4,5,6-pentachlorophenol)

CAS Registry Number: 87-86-5

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.1 mg/m^3**
Oral reference exposure level	**0.03 mg/kg/day (U.S. EPA RfD)**
Critical effect(s)	Hepatic and renal toxicity including elevated serum glutamic pyruvic transaminase, pigmentation of the liver and kidneys, increased liver and kidney weight, hepatic enzyme induction and centrilobular vacuolization, hepatic hyperplasia and porphyria in rats.
Hazard index target(s)	Alimentary system; kidney; teratogenicity

II. Physical and Chemical Properties (ATSDR, 1992)

Molecular formula	C_6HCl_5O
Molecular weight	266.35 g/mole
Specific gravity	1.978 @ 22° C/4° C
Boiling point	309-310° C
Vapor pressure	0.00011 mm Hg @ 25° C, 0.12 mm Hg @ 100° C
Solubility	5 mg/l in water @ 0° C, 14 mg/l in water @ 20° C, 20 mg/l in water @ 30° C, 35 mg/l in water @ 50° C, 85 mg/l in water @ 70° C, Soluble in most organic solvents
Log K_{ow}	5.12
Log K_{oc}	Measured Koc= 3000-4000

III. Major Uses and Sources (HSDB, 1995)

Previously pentachlorophenol (PCP) has been used in large quantities as an insecticide and fungicide in preserving wood products and in smaller quantities as a molluscicide, for use in the preservation of starches, dextrins, and glues. PCP has been used in the treatment of cable coverings, canvas belting and nets, incorporated into paints, pulp stock especially for paper, in

hardboard and particle board, as a soil fumigant for termites, as a herbicide for weeds, as a preharvest defoliant for seed crops, for treatment of seeds (especially beans), as a herbicide for control of moss on lawns and roofs, as a fungicide on prunes, as a preservative for leather, textiles and inks, as a slimicide and algacide, as an antibacterial agent in disinfectants and cleaners, and other uses. It is used in pressure treatment of lumber at 5% concentration. Many commercial products containing PCP have also been found to be contaminated with polychlorinated dibenzodioxins and dibenzofurans, (predominantly hexa-, hepta-, and octachlorinated congeners) as by-products of pentachlorophenol synthesis. Thus, many commercial uses of PCP are being phased out.

IV. Effects of Human Exposure

Numerous studies have been published regarding toxicological and epidemiological findings following PCP exposure in humans. Chronic PCP poisoning can be difficult to detect since the symptoms are often vague: anorexia, weight loss, general weakness, dizziness, obstinate headache, personality changes or anxiety (Jorens and Schepens, 1993). However, the clinical features of acute and chronic PCP poisoning can be classified by their effects on skin, energy metabolism (fever), hematopoietic tissue, respiratory system, nervous system (central and peripheral), kidney and gastro-intestinal tract. An investigation of 10 workers employed in the PCP production department of an East German plant determined that the early effects of PCP included eye irritation and bronchitis (Baader and Bauer, 1951). Chronic symptoms of toxicity, which began several months after the beginning of PCP production, included severe skin eruptions and neuralogic pain in the lower extremities. Some workers also exhibited bursitis of the elbow, palpitations, disturbance of libido and weakness of the lower limbs. A large scale study of occupational exposure to PCP at a plant between 1953 and 1978 found 47 cases of chloracne out of a total of 648 workers (O'Malley *et al.*, 1990). Workers that had direct skin contact with PCP had a significantly increased risk of developing chloracne (a classic effect of clorinated dioxin exposure) compared to workers who did not. A fatal case of aplastic anemia was reported following heavy exposure for 1 year to wet lumber processed with a wood preservative containing 3% PCP and 1. 5% tetrachlorophenol (Roberts, 1963). The worker also had splenomegaly when first admitted to the hospital, suggesting exposure to a toxic agent. Other cases of aplastic anemia (Roberts, 1983) and pure red cell agenesis (Schmid *et al.*, 1963) following PCP exposure have been reported. The renal function of 18 employees of a PCP plant improved following a 20 day vacation (Begley *et al.*, 1977). Creatinine clearance and phosphate reabsorption was lower before the vacation than after the vacation, indicating that PCP reduces both glomerular filtration rate and tubular function. A 2-year study of the occupational exposure of lumber mill workers to a wood preservative containing PCP and tetrachlorophenol found no statistically significant relationship between the number of health problems reported and the mean urinary levels of PCP (Kleinman *et al.*, 1986). Urinary levels of PCP ranged from 69 to 103 ppb. Workers handling wet treated wood tended to have higher levels of urinary PCP indicating skin contact to be an important route of exposure. Another study of workers occupationally exposed to PCP in wood preservatives 0.33 to 26.3 years (median, 6.5 years) found no adverse health effects or increased incidence of mortality (Gilbert *et al.*, 1990). However, urinary levels of PCP in workers (174 ppb) were significantly greater than that of controls (35 ppb). The

formation of unwanted contaminants, such as dioxins and furans, can occur during the synthesis of PCP. Some of these contaminants are highly toxic. It is quite possible, particularly in the older human-case studies, that at least some of effects attributed to PCP may actually be due to contaminants in PCP (Jorens and Schepens, 1993).

V. Effects of Animal Exposure

Target organs affected by chronic PCP exposure include the liver, the kidney, and the immune system. PCP has also been reported to be fetotoxic. The immunotoxicity of PCP reported in the literature may be due partially or in full to the polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) impurities present in technical grade PCP. Purified PCP contains lower levels of these impurities than the technical grade PCP and appears to possess little immunotoxic activity itself.

A number of chronic and subchronic studies concentrating on effects in the kidney and liver have been conducted using various PCP preparations and include those by Schwertz *et al.* (1978), Knudsen *et al.* (1974), Kimbrough and Linder (1978), Johnson *et al.* (1973), Greichus *et al.* (1979), Kerkvliet *et al.* (1982), McConnell *et al.* (1980), Nishimura *et al.* (1980), and NTP (1989). Schwetz *et al.* (1978), treated rats by oral administration of Dowicide EC-7 (90% pure PCP) in feed at doses of 0, 3, 10, or 30 mg/kg/day for 2 years. The Dowicide EC-7 administered contained lower levels of impurities than technical grade PCP. Pigmentation of the liver and kidneys was observed at the 10 and 30 mg/kg/day doses and animals administered 30 mg/kg/day, exhibited signs of reduced body weight gain, elevated serum glutamic pyruvic transaminase (SGPT) levels, and increased kidney weight. The pigmentation of the liver and kidneys is of unknown significance (ATSDR, 1992). The observed chronic NOAEL in this study for liver and kidney effects in rats is 3 mg/kg/day and the chronic LOAEL is 10 mg/kg/day. Greichus *et al.* (1979) reported a NOAEL for liver effects of 5 mg/kg/day and a LOAEL of 10 mg/kg/day based upon administration of purified PCP in capsules to pigs at levels of 5-15 mg/kg/day, for 30 days. Changes observed include non-specific diffuse cloudy hepatocellular swelling and transient increased blood urea nitrogen. Kimbrough and Linder (1978) tested both purified and technical grade PCP in rats at doses of 1-25 mg/kg/day, 7 days/week for 8 months. Histopathological changes observed in rats administered purified PCP include slightly enlarged hepatocytes and pigmented Kupffer cells. Rats administered technical grade PCP exhibited changes which included fibrosis, enlarged pleomorphic hepatocytes, vacuolization, hyperplasia, and porphyria. In this study Kimbrough and Linder (1978) observed a NOAEL for purified PCP for liver effects in rats of 5 mg/kg/day and a NOAEL of 1 mg/kg/day for technical grade PCP. Knudsen *et al.* (1974) also observed hepatic effects similar to those occurring with technical grade PCP when rats were feed 1.25-10 mg/kg/day PCP containing the dioxin isomer octachlorodibenzo-p-dioxin (OCDD). Observed effects included increased liver weight, increased enzyme activity, and centrilobular vacuolization. In a subchronic study reported by Johnson *et al.* (1973), rats were administered technical grade or purified PCP in feed at levels ranging between 3-300 mg/kg/day for 90 days. Increased liver weights and histopathological changes (minimal focal hepatocellular degeneration and necrosis) were observed in animals administered technical grade PCP while animals in the purified PCP treatment groups displayed

increased liver weights only (histopathological effects were not observed). Kidney weight changes were noted in animals administered either grade of PCP. A LOAEL for liver effects of 6.5 mg/kg/day in mice administered purified and technical grade PCP in feed for 7 days/week, 10-12 weeks was reported by Kerkvliet *et al.* (1982). McConnell *et al.* (1980), administered 15-20 mg/kg/day of either technical grade or purified PCP to cows in their feed. Dietary technical grade PCP increased liver weight, generated minimal histopathological hepatic lesions, and increased enzyme activity, while in contrast cows receiving purified PCP exhibited a smaller increase in hepatic enzyme activity without accompanying histopathologic lesions. Based on the results of this study, a LOAEL for liver effects in cows is 15-20 mg/kg/day. Nishimura *et al.* (1980) observed hepatic effects in rats administered technical PCP by gavage at doses of 40-160 mg/kg/day, 2 times/week for 1-3 months. Observed effects included increased liver weight, increases in serum LDH, SGPT, and serum glutamic oxaloacetic transaminase (SGOT) levels, hepatocellular swelling, and vacuolization. Hepatic effects were also reported by NTP (1989) in a 30 day and 6 month study of mice administered one of three PCP preparations: technical grade, Dowicide EC-7 (containing lower levels of impurities than technical grade PCP), or purified PCP. Histopathological changes were observed due to all three preparations.

More recently, a number of studies have examined the effects of PCP on the immune system. Studies of the immune system of rats administered technical grade or purified PCP indicate that the technical grade affects a range of immune parameters (humoral and cellular immunity, and complement activity) while generally PCP itself appears to possess little immunotoxic activity. Kerkvliet *et al.* (1985a) administered technical grade or purified PCP to rats, 7 days/week for 6 weeks. Technical grade PCP induced a dose-related suppression of antibody response (sheep red blood cell challenge) in animals receiving doses of 0.5 mg/kg/day and above while rats receiving purified PCP did not exhibit this response. Similar results were observed in mice administered technical grade and purified PCP. Co-administration of heptachlorodibenzo-p-dioxin (HpCDD), a prevalent dioxin impurity found in technical PCP, with purified PCP in rats resulted in an immunosuppressive response similar to that seen with technical PCP. In another study conducted by Kerkvliet *et al.* (1985b), mice were administered technical PCP in their diet for 8 weeks prior to *in vitro* immune function tests. These tests indicate that T-cell and macrophage activity are not affected by administration of technical PCP, in contrast to the previous findings that technical PCP adversely affects humoral immunity in rats. In 1982, Kerkvliet *et al.* reported the results of a study in which mice were fed technical and purified PCP for 10-12 weeks. The results indicate a LOAEL for technical grade PCP of 2.5 mg/kg/day and a LOAEL for purified PCP of 25 mg/kg/day, indicating that the immunomodulatory effects observed were due primarily to the contaminants present in the technical grade. Forsell *et al.* (1981) administered technical PCP in feed to cattle for 130 days at doses of 0.2-2 mg/kg/day. Significant changes in the immunological parameters evaluated were not observed.

Developmental and reproductive effects have been noted in animals dosed with PCP. Pregnant rats were administered 0, 3, 10, or 30 mg/kg/day PCP in their diet for 62 days and then exposed during mating, gestation, and lactation (Schwetz *et al.* 1978). Adverse effects on fetuses and dams were not observed in animals administered a dose of 3 mg/kg/day. At an administered dose of 30 mg/kg/day, the following effects were observed: decreased body weight in adult animals, increased number of litters with variations in development of skeletal structures, decreased

average litter size, decreased neonatal survival, and decreased mean neonatal body weights. A NOAEL of 3 mg/kg/day is reported for developmental toxicity in rats. Schwetz *et al.* (1974) administered technical and purified PCP to pregnant rats at levels up to 50 mg/kg/day on days 6-15, 8-11, or 12-15 of gestation. Maternal and fetotoxic (fetal anomalies, resorptions, and body measurements) effects due to both grades of PCP were more pronounced following treatment during early (days 8-11) rather than later (days 12-15) organogenesis. Administration of purified PCP resulted in an increased incidence of delayed ossification of the skull bones. Teratogenic effects were not observed. This study reports a NOAEL for developmental effects for technical PCP of 5.8 mg/kg/day, which is equivalent to 5 mg/kg/day of purified PCP. Courtney *et al.* (1976) reported that decreased average fetal weight was the only effect observed in a study of pregnant rats administered 75 mg/kg/day PCP (unknown purity) on days 7-18 of gestation. Welsh *et al.* (1987) administered purified PCP to male and female rats at doses up to 43 mg/kg/day in diet for 181 days. Evidence of fetal and maternal toxicity was observed at the highest dose. At 13 mg/kg/day, male fetuses had decreased body weights. This study reports a NOAEL for developmental effects for purified PCP of 4 mg/kg/day.

VI. Derivation of U.S. EPA Reference Dose (RfD)

Study	Schwetz *et al.* (1978)
Study population	Male and female Sprague-Dawley rats 25 rats/sex/dose level
Exposure method	Diet (3, 10, and 30 mg/kg-bw)
Critical Effects	Hepatic and renal toxicity including elevated serum glutamic pyruvate transaminase, pigmentation of the liver and kidneys, increased urine specific gravity
LOAEL	10 mg/kg/day
NOAEL	3 mg/kg/day
Exposure continuity	Continuous
Exposure duration	24 months females, 22 months males
Average exposure concentration	0, 3, 10, 30 mg/kg/day
Subchronic uncertainty factor	1
LOAEL uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Oral reference exposure level	0.03 mg/kg/day (U.S. EPA RfD)
Route-to-route extrapolation factor	3.5 mg/m^3 per mg/kg/day
Inhalation reference exposure level	0.1 mg/m^3 (100 $\mu g/m^3$)

The known toxic effects of PCP include hepatotoxicity, renal toxicity, immunotoxicity and developmental toxicity. Examining the various studies available it was noted that hepatic toxicity and renal toxicity were consistent findings. Studies available on the reproductive and developmental toxicity indicated an observed NOAEL which was not lower than that for the liver

and kidney where there is a larger data base available. Immunotoxic effects are observed for pentachlorophenol, however the NOAEL for purified pentachlorophenol in some of these studies was approximately ten times that for liver and kidney effects. Furthermore, studies in rodents detect an immunological effect while another study in cows did not detect an immunotoxic effect suggesting that there could be species differences for this endpoint. The basis for the chronic REL for pentachlorophenol is the Schwetz *et al.* (1978) study which indicates a chronic oral in rats NOAEL of 3 mg/kg/day, based on liver and kidney effects. Assuming an uncertainty factor of 100 to account for interspecies variability and protection of sensitive human populations, an oral reference exposure level of 0.03 mg/kg/day is obtained. This value is equivalent to an inhalation REL of 100 $\mu g/m^3$ (assuming a daily respiration rate of 20 m^3 of air and an average body weight of 70 kg).

The strengths of the inhalation REL include the availability of chronic exposure data from a well-conducted study with histopathological analysis and the observation of a NOAEL.
Major areas of uncertainty are the lack of adequate human exposure data and the lack of inhalation exposure studies.

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CHRONIC TOXICITY SUMMARY

PHENOL

(Carbolic acid, phenylic acid, phenyl hydroxide)

CAS Registry Number: 108-95-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**600 µg/m^3**
Critical effect(s)	Twitching, muscle tremors, neurological impairment; elevated serum liver enzymes in rats
Hazard index target(s)	Alimentary system; circulatory system; kidney; nervous system

II. Physical and Chemical Properties (From HSDB, 1995; ATSDR, 1989)

Molecular formula	C_6H_5OH
Molecular weight	94.11 g/mol
Description	Colorless to light pink solid
Specific gravity	1.0576 @ 20° C
Boiling point	181.75° C
Vapor pressure	0.3513 torr @ 25° C
Solubility	86,000 ppm in water, very soluble in alcohol, carbon tetrachloride, acetic acid and liquid sulfur dioxide; soluble in chloroform, ethyl ether, carbon disulfide; slightly soluble in benzene
Henry's Law Constant	3.97 x 10^{-7} ATM-m^3 /mol (25 °C)
Conversion factor	1 ppm = 3.85 mg/m^3

III. Major Uses or Sources (HSDB, 1995)

Phenol is obtained from coal tar and is widely used as a disinfectant for industrial and medical applications. It also serves as a chemical intermediate for manufacture of nylon 6 and other man-made fibers and for manufacture of epoxy and other phenolic resins and as a solvent for petroleum refining. Approximately half of the U.S. consumption is directly related to the housing and construction industries, in applications such as germicidal paints and slimicides.

IV. Effects of Human Exposures

The information that is available concerning the health effects of phenol exposure to humans is almost exclusively limited to case reports of acute effects of either oral exposure (Bruce *et al.*, 1987), or dermal exposure (Griffiths, 1973), or from occupational exposures, for some of which exposure is by inhalation (Dosemeci *et al.*, 1991; Ohtsuji and Ikeda, 1972; Connecticut Bureau of Industrial Hygiene). Data in animals is consistent with human data and shows phenol to be well absorbed by oral, dermal, and inhalation routes of exposure. Severe chronic poisoning manifests in systemic disorders such as digestive disturbances including vomiting, difficulty swallowing, ptyalism (excess secretion of saliva), diarrhea, and anorexia (Bruce *et al.*, 1987; Baker *et al.*, 1978). Phenol poisoning is associated with headache, fainting, vertigo, and mental disturbances (Bruce *et al.*, 1987; Gosselin *et al.* 1984) which are likely symptoms of neurological effects well documented in animal studies. Ochronosis, or discoloration of the skin and other dermatological disorders may result from dermal phenol exposure (Deichmann and Keplinger, 1962; Bruce *et al.*, 1987). Several investigators (Truppman and Ellenby, 1979; Warner and Harper, 1985) have reported that the use of phenol in the surgical procedure of skin peeling can produce cardiac arrhythmias although specifics of dose received were not determined and would be expected to be high.

The number of human exposure studies in which populations were exposed to phenol over longer periods of time (subchronic and chronic) are limited and have serious deficiencies including multiple chemical exposures, in many cases small size of exposed populations, and lack of information on dose received.

Occupational studies make up the majority of subchronic/chronic studies available on human health effects associated with phenol exposure. Merliss (1972) described muscle pain and weakness of unknown etiology, enlarged liver, and elevated serum enzymes (LDH, GOT, and GPT) characteristic of liver damage in an individual with intermittent inhalation and dermal exposures to phenol, cresol and xylenol. Bruze (1985) noted that a number of phenol-formaldehyde based resins are dermal irritants and contact sensitizers. Johnson *et al.* (1985) examined 78 iron and steel foundry workers with multiple chemical and aerosol exposures that included phenol and found more respiratory symptoms in the phenol exposed group. However, multiple exposure to diphenyl methane diisocyanate, formaldehyde, and silica containing aerosols prevented determination of the effects of phenol. Baj *et al.* (1994) examined twenty two office workers exposed for six months via inhalation to a commercial product containing formaldehyde, phenol and chlorohydrocarbons. At the end of the six month period the indoor air of the workers contained 1,300 $\mu g/m^3$ of formaldehyde and 800 $\mu g/m^3$ of phenol. The eight workers with the highest concentrations of phenol in their urine had decreased erythrocyte and T-helper lymphocyte numbers and increased numbers of eosinophils and monocytes compared to controls. The multiple chemical exposure of this study prevents concluding these effects are attributable to phenol exposure. NIOSH (1984) in a study of hospital workers documented dermal effects in workers exposed to a number of chemicals including phenols contained in disinfectants. This study however could not document any differences in urinary levels of phenol metabolites between control populations and exposed populations and could not assign any of the dermal effects seen to phenol or other substances in the work environment. Dosemeci

et al (1991) conducted a follow-up study to evaluate mortality in 14,861 workers in five manufacturing facilities producing or using phenol and formaldehyde. Arteriosclerotic heart disease, emphysema, disease of the digestive system, and cirrhosis of the liver were found to be inversely related to the extent of phenol exposure. Due to multiple chemical exposures the effects of phenol alone could not be identified with any certainty.

Baker *et al.* (1978) completed a study of 39 individuals exposed to drinking water contaminated with phenol for a period of 4-8 weeks. Doses of phenol were estimated to range between 10 mg/day and 240 mg/day. Effects seen included increased incidence of diarrhea, mouth sores and irritation of the oral cavity.

Two occupational studies are of note since they reported NOAELs. Workers exposed continuously for an unspecified period of time to an average air concentration of 4 ppm phenol experienced no respiratory irritation (Connecticut Bureau of Industrial Hygiene). No adverse effects were reported among workers in a Bakelite factory who were exposed to 3.3 ppm (Ohtsuji and Ikeda, 1972). In this study urinary phenol levels were measured and were observed to return to pre-exposure levels with 16 hours after exposure indicating a relatively rapid clearance of phenol from the body that was confirmed in a study by Piotrowski (1971).

V. Effects of Animal Exposures

In animal studies a number of subchronic and chronic studies employing oral and inhalation routes of exposure are available as well as shorter term studies using the dermal route of exposure. Responses observed in animal studies include: pulmonary damage (inhalation exposure), myocardial injury (inhalation and dermal exposure), liver damage (inhalation exposure), renal damage (inhalation exposure), neurological effects (inhalation exposure), developmental effects (oral exposure) and dermal effects (dermal exposure). Comparison of the three routes of exposure found that oral exposure was less effective at producing systemic toxic effects possibly due to the rapid metabolism of phenol to sulfate and glucuronide conjugates by the gastrointestinal tract. Comparison of health effects between studies using dermal, oral and inhalation routes of exposure finds that inhalation is a sensitive route of exposure for laboratory animals.

Several subchronic inhalation studies of health effects from phenol exposure are available but no inhalation studies longer than 90 days could be identified. Deichmann *et al.* (1944) exposed guinea pigs, rats, and rabbits to concentrations of phenol between 26 and 52 ppm for 28-88 days depending on species. Guinea pigs exposed for 7 hours per day, five days per week, for four weeks, displayed signs of respiratory difficulty and paralysis affecting primarily the hind quarters indicating neurological effects. Five of twelve animals exposed at this concentration died at 28 days. At necropsy, extensive myocardial necrosis, lobular pneumonia, fatty degeneration of the liver, and centrilobular hepatocellular necrosis were observed in all animals exposed at this level. Guinea pigs sacrificed at 41 days also exhibited pulmonary inflammation, pneumonia, bronchitis, endothelial hyperplasia, and capillary thrombosis. Rabbits exposed at these same concentrations did not exhibit any signs of discomfort, but showed similar findings at necropsy at 88 days. Rats

were less sensitive in this study with an apparent NOAEL of 26 ppm phenol for these effects. In this study, guinea pigs were the most sensitive species. Limitations of the Deichmann study include a range of exposure concentrations and a lack of a control group. Sandage (1961) exposed Sprague-Dawley rats, mice and rhesus monkeys for 90 days continuously to a 5 ppm concentration of phenol. Sandage found no effects on pulmonary, cardiovascular, hematological, hepatic, or renal systems, thus defining free-standing NOAELs for these systemic effects in these species. Limitations of this study include absence of guinea pigs previously identified as the most sensitive species in the Deichmann study and lack of a demonstrated dose response to the effects of phenol. Dalin and Kristofferson (1974) examined the effects of phenol on the nervous system in rats exposed continuously for 15 days to a concentration of 26 ppm phenol and found muscle tremors, twitching and disturbances in walking rhythm and posture after 3-5 days exposure. After 15 days exposure, severe neurological impairment as measured by decreased performance on tilting plan test was found. The Dalin and Kristofferson (1974) study also documented elevated serum concentrations of LDH, GOT, GPT, and GDH indicative of liver damage in animals exposed to 26 ppm phenol continuously for 15 days.

The NCI (1980) study of the carcinogenicity of phenol is the most complete chronic study using the oral route of exposure. Mice and rats were exposed for 103 weeks to concentrations of phenol in their drinking water of 100, 2500, 5000, and 10,000 ppm. NOAELs in the mouse of 523 mg/kg/day (5000 ppm in drinking water) and NOAELs in the rat of 630 mg/kg/day (5000 ppm in drinking water) were observed for effects on the respiratory system, cardiovascular system, gastrointestinal system, hepatic system, renal system, and the brain based on histological examination of tissues. Male rats exposed to the 5000 ppm had a higher incidence of kidney inflammation (94%) than controls (74%) and no tests of kidney function were performed in this study so the 5000 ppm exposure may not represent a NOAEL for renal effects in this study.

Boutwell and Bosch (1959) reported on the results of a chronic study in mice involving skin painting of 1.2 mg phenol or 2.5 mg phenol for a 52 week period. A NOAEL of 1.2 mg/animal for a 52 week exposure for dermal effects was found.

No multi-generational studies evaluating reproductive or developmental effects under chronic exposure conditions could be identified. Jones-Price *et al.* (1983a) reported that pregnant rats dosed orally with 0, 30, 60, and 120 mg/kg/day on gestation days 6-15 exhibited reduced fetal weight in a dose-related manner. However, no teratogenic effects or fetal deaths were observed. In a following study (Jones-Price *et al.*, 1983b) reported that pregnant rats dosed orally with 0, 70, 140, and 280 mg/kg/day on gestation days 6-15 exhibited decreased maternal weight gain, tremors, and increased maternal mortality at the 280 mg/kg/day dose. In the fetus reduced growth, decreased viability, and increased incidence of cleft palate were seen at the 280 mg/kg/day dose.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Sandage, 1961; Dalin and Kristofferson, 1974
Study population	Mice, Sprague Dawley rats and rhesus monkeys
Exposure method	Continuous inhalation
Critical effects	Systemic effects including liver and nervous system effects
LOAEL	26 ppm (Dalin and Kristofferson, 1974)
NOAEL	5 ppm (Sandage, 1961
Exposure Continuity	Continuous
Average exposure concentration	5 ppm for NOAEL group
Human equivalent concentration	5 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Exposure duration	90 days
Subchronic uncertainty factor	1
LOAEL uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.2 ppm (200 ppb; 0.6 mg/m^3 (600 μg/m^3)

No suitable human studies were available for use since all exposures were either short term or occupational in nature or did not determine dose. Of the three routes of exposure available, inhalation appears to be the most sensitive based on the number and intensity of systemic effects noted (Deichmann *et al.*, 1944) relative to oral exposure (NCI, 1980). In support of this ATSDR (1989) notes that the gastrointestinal tract has a large capacity to metabolize phenol to sulfate and glucuronide conjugates which appear likely to be less toxic than the parent compound, thus NOAELs derived from oral studies may not be applicable for other routes of exposure. The Deichmann *et al.* (1944) study identified guinea pigs as being the most sensitive species, however, this study had a number of serious deficiencies including absence of controls, significant variability in the concentrations of phenol used in their exposure, and exposure that was not continuous. Since alternative studies using guinea pigs could not be identified, the rat was chosen as an alternative species based on the rat having the most similar metabolic profile for metabolism of phenol of that of humans (ATSDR, 1989; Capel *et al.*, 1972). The Sandage (1961) study was chosen over other available studies due to it being the longest in duration (90 days), having a continuos exposure and evaluating three species (rats, mice, monkey). NOAELs determined in the Sandage study for systemic effects in all three species examined were 5 ppm, consistent with the idea that 5 ppm is a NOAEL for a number of species. Although this is a free-standing NOAEL, a subsequent study in rats indicated that nervous system and hepatic effects occur at a concentration of 26 ppm after several days (Dalin and Kristofferson, 1974).

The 5.0 ppm standard for phenol in the work place (ACGIH, 1988; OSHA, 1985; NIOSH, 1976) is considered protective of the health of workers exposed occupationally but does not consider sensitive populations and is not for continuous exposure conditions.

The major strength of the key study is the observation of a NOAEL from subchronic continuous exposure study involving exposure of several different species. The primary uncertainties are the lack of adequate human health effects data, the lack of multiple concentration inhalation exposure studies demonstrating a dose-response relationship, and the lack of studies with guinea pigs which have previously been identified as a sensitive species.

VII. References

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CHRONIC TOXICITY SUMMARY

PHOSGENE

(Carbon dichloride oxide, Carbon oxychloride, Carbone (oxochlorure de) (French), Carbonic acid dichloride, Carbonic dichloride, Carbonio (ossicloruro di) (Italian), Carbonyl chloride, Carbonyl dichloride, Carbonylchlorid (German), Chloroformyl chloride, Fosgen (Polish), Fosgene (Italian), Koolstofoxychloride (Dutch), Phosgen, GVG)

CAS Registry Number: 75-44-5

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.3 µg/m^3**
Critical effect(s)	Pulmonary toxicity in rats including: widening of pulmonary interstices and accumulations of foamy cells at the transition from terminal bronchioles to alveolar ducts. Increased protein content of pulmonary lavage fluid indicating changes in pulmonary membrane permeability and/or inflammatory response.
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties (HSDB, 1995)

Description	Colorless gas
Molecular formula	$COCl_2$
Molecular weight	98.92 g/mol
Melting point	-118°C
Boiling point	8.2°C @ 760 mm Hg
Vapor pressure	1215 mm Hg @ 20°C; 568 mm Hg @ 0°C
Solubility	Slightly soluble in water; freely soluble in benzene, toluene, glacial acetic acid, chloroform, and most liquid hydrocarbons.
Conversion factor	1 ppb = 4.0 mg/m^3

III. Major Uses or Sources (HSDB, 1995)

Initially developed as a war gas, phosgene is now used in the preparation of many organic chemicals. It is used as an intermediate carbonylating agent and in the production of aniline dyes. Phosgene is used in the manufacture of dyestuffs based on triphenylmethane, coal tar and urea, isocyanates and their derivatives, i.e., carbonic acid esters and acid chlorides. Phosgene is

used in smaller quantities to manufacture some insecticides and pharmaceuticals and in metallurgy. A rough breakdown of phosgene consumption estimated 62% is used to produce toluene diisocyanate, 24% to produce polymethylene polyphenylisocyanate, 4% to make polycarbonate resins and 10% in miscellaneous uses. The US demand for phosgene in 1991 was roughly 2 billion pounds. Phosgene is also produced from the breakdown of chlorinated hydrocarbons in the presence of short wavelength ultraviolet radiation such as occurs in heliarc welding of aluminum as well as in the breakdown of chlorinated hydrocarbons in the presence of hot iron and oxygen such as occurs in the welding of degreased steel. Additionally, chlorinated hydrocarbons including carbon tetrachloride, chloroform, and methylene chloride will decompose to phosgene in the presence of fire or heat.

IV. Effects of Human Exposures

Much of the data on human exposures to phosgene comes from the military as a result of phosgene's initial use as a war gas and from industrial settings where phosgene is used as an intermediate carbonylating agent in industrial chemical synthesis. The potent acute toxic effects of phosgene, coupled with a mechanism of action which involves direct acylation of biological molecules (Diller, 1985a), have focused toxicity testing on acute effects to the lung which historically has been considered to be the principal target tissue for inhaled phosgene. There is no quantitative data available on the chronic toxic effects of the compound in humans (American Conference of Governmental Industrial Hygienists, 1989). Case reports of poisoning in humans indicate that exposed individuals may not avoid lethal exposures due to an odor threshold (0.9 ppm) (American Industrial Hygiene Association, 1989) which is well above levels that are toxic, combined with a relatively short period of time necessary for a lethal exposure; i.e., levels greater than 62 ppm for 30 min. or more may be fatal (Thienes and Haley, 1972). Death may occur from delayed pulmonary edema and cardiorespiratory arrest. Persons recovering from acute exposure usually make a relatively complete recovery after several months to several years (Diller, 1985b). For a review of the acute effects of phosgene in humans and an acute REL, please see OEHHA (1995).

V. Effects of Animal Exposures

The majority of information available on the toxicity of phosgene to laboratory animals is from single dose experiments. A fewer number of investigators performed experiments employing multiple doses; the longest dosing period was 12 weeks in a study on the effects of phosgene exposure in dogs (Rossing, 1964). To date no studies are available for chronic exposure to phosgene in laboratory animals. Therefore this summary includes information from both acute and subacute studies with emphasis on studies with longer periods of dosing and/or greater numbers of individual doses and information on studies that identified a NOAEL or LOAEL.

The lung has been repeatedly shown to be the principal target organ for the toxic effects of inhaled phosgene. A number of effects were noted in studies employing a single dose or a few doses. Phosgene alters pulmonary immune system function. Phosgene suppresses pulmonary

natural killer cell activity in Fischer 344 rats exposed to 0.5 or 1.0 ppm for 4 hours and does not suppress pulmonary natural killer cell activity in rats exposed to 0.1 ppm for 4 hours (Burleson and Keys, 1989). Ehrlich and Burleson (1991) found exposure of rats to 1 ppm phosgene for 4 hours significantly enhanced and prolonged pulmonary influenza virus infection 3 and 4 days after phosgene exposure and concomitant inoculation with influenza virus. Phosgene exposure increased streptococcal infection in mice exposed to *Streptococcus zooepidemicus* and 0.025 ppm phosgene for 4 hours, while mice exposed to 0.01 ppm for 8 hours did not have an increased incidence of streptococcal infection (U.S. EPA, 1989). Phosgene exposure has been found to produce a number of changes in the lung related to changes in membrane permeability. Currie *et al.* (1987a) examined body weight, lung wet weight, lung dry weight, lung lavage fluid protein, total cell count in lavage fluid and differential counts in lavage fluid from male Sprague-Dawley rats exposed to concentrations ranging between 0.125 and 1.0 ppm for 4 hours. The rats were examined at the conclusion of exposure and for 3 days post exposure. Higher concentrations of phosgene (1.0 and 0.5 ppm) significantly changed body weights, lung wet weights, lung dry weights, and lavage fluid protein at various times after exposure. Levels of lavage fluid protein were not significantly different from control by day two after exposure to the 0.25 ppm concentration. Currie *et al.* (1987b) found that phosgene significantly reduced pulmonary ATP levels immediately after exposure of male Sprague-Dawley rats to 0.05 ppm, 0.125 ppm, 0.25 ppm, 0.5 ppm and 1.0 ppm phosgene. Pulmonary ATP levels significantly increased for days 2 and 3 postexposure for the 1.0 ppm exposure group. Diller *et al.* (1985) administered concentrations of phosgene between 0.1 ppm and 5.0 ppm to Wistar rats for periods ranging between 10 and 500 minutes. At the lowest concentration (0.1 ppm) and longest duration of exposure (500 min.) phosgene increased pulmonary lavage protein levels, widened pulmonary interstices and accumulations of foamy cells at the transition from terminal bronchioles to alveolar dusts were found.

With regard to longer term studies and studies with multiple doses, Cameron and Foss (1941) exposed mice, rats, rabbits, cats and goats to 1.1 ppm phosgene for 5 hours per day for 5 days and found that all animals had some degree of edema in the lungs. Severe pulmonary lesions in cats, rabbits, guinea pigs, and mice were noted, while rats and goats appeared to be less affected. Cordier and Cordier (1953) exposed cats and guinea pigs to 2.5 to 6.25 ppm for 10 min. per day for 2 to 41 days and found pulmonary edema, bronchitis, bronchopneumonia and lethality. Rossing (1964) exposed mongrel dogs to 24-40 ppm phosgene for 30 min. per day, 1-3 times per week for up to 12 weeks and found up to a 20-fold increase in airway resistance with increase in exposure. It is of note that these studies all employed exposure concentrations greater than those used in acute studies and recorded “severe” effects.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Diller *et al.* (1985)
Study population	Male albino Wistar rats (160-180 g; 10-15/treatment group).
Exposure method	Continuous inhalation exposure (0, 0.1, 0.15, 0.25, 1.0, and 5.0 ppm)
Critical effects	Pulmonary toxicity including: widening of pulmonary interstices and accumulations of foamy cells at the transition from terminal bronchioles to alveolar ducts. Increased protein content of pulmonary lavage fluid indicating changes in pulmonary membrane permeability and/or inflammatory response.
LOAEL	0.1 ppm
NOAEL	Not observed
Exposure continuity	Single exposure
Exposure duration	4 hours for all concentrations, also 8 hours, 20 minutes for the 0.1 ppm concentration.
Average exposure concentration	0.1 ppm for LOAEL group
Human equivalent concentration	0.15 ppm for LOAEL group (gas with pulmonary respiratory effects, RGDR = 1.5, based on 170 g body weight, MV = 0.13 L/min, SA(PU) = 3,400 cm^2)
Subchronic uncertainty factor	10
LOAEL uncertainty factor	10
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	3,000
Inhalation reference exposure level	0.00005 ppm (0.05 ppb; 0.0003 mg/m^3; 0.3 $\mu g/m^3$)

No chronic toxicity data are available for this compound in either animal models or humans necessitating the estimation of a reference exposure level based on an acute or subacute NOAEL or LOAEL in an animal model. Phosgene has the potential to cause delayed toxic effects. Gross *et al.* (1965) reported that rats exposed to 2 ppm of phosgene for 80 min. exhibited lung abnormalities 3 months after exposure. Rossing (1964) reported emphysema and obliterative bronchiolitis in dogs after 12 weeks exposure to phosgene. Gladstron *et al.* (1947) reported long term lung disease in people exposed to phosgene although no dose was specified. The severity of pulmonary damage has been correlated with the product of concentration x time or Ct factor by Haber (1924) and others including Gross *et al.*(1965) suggesting that exposure to lower concentrations for longer periods of time can be potentially damaging. A protective effect of initial phosgene exposure to subsequent exposures has been noted, however, development of tolerance is believed to be a triggering mechanism for chronic irreversible lung damage (American Conference of Governmental Industrial Hygienists, 1989) and information on

acquired tolerance in man is unavailable (Cucinell, 1974). Furthermore, Cucinell (1974) argues, on the basis of available toxicity data, data on the effects of temperature on the toxicity of phosgene, the presence of susceptible human populations, and differences in exposure time between occupational and chronic human exposures, that the occupational Threshold Limit Value (TLV) for phosgene of 0.1 ppm for an 8 hour work day is too high. Additionally he notes that a reference exposure level should include a factor of 10 for extrapolation of a LOAEL to a NOAEL, a factor of 10 for sensitive human populations, and a factor of three for time differences between occupationally exposed individuals and chronically exposed individuals.

The Diller *et al.* (1985) study was chosen for setting a REL based on a number of factors. The study employed a relatively long exposure of 8 hours and 20 min. at concentrations of phosgene as low as 0.1 ppm. The 0.1 ppm exposure is lower than that used in longer term studies (see above) where overt toxic effects were noted. More recent acute studies identify NOAEL's of 0.1 ppm for pulmonary immunocompetence (Burleson and Keys, 1989) and 0.125 ppm for no elevation in the level of protein in lung lavage fluids suggesting that the Diller *et al.* (1985) study was more sensitive. The study by Currie *et al.* (1987b) found a NOAEL of 0.05 ppm for changes in lung ATP levels, however this study was not used due to uncertainty over whether or not changes in pulmonary ATP levels represented a protective biochemical response or a pathological effect. Both histopathological and biochemical indices of toxicity were examined in the Diller *et al.* (1985) study giving a higher level of confidence that the responses noted were reflective of potential chronic toxic effects. There was also evidence of a dose response in this study.

A subchronic uncertainty factor of 10 was employed to correct for differences in the length of exposure between this study and a lifetime exposure in this species (a linear time-weighted average correction would be a factor of 2,100) and the observation that the cumulative dose of phosgene appears to be important (see above). An interspecies uncertainty factor of 10 was employed based on the data of Cameron and Foss (1941) suggesting that rats may represent a more resistant species.

The strengths of the inhalation REL include the availability of controlled exposure inhalation studies at multiple exposure concentrations. Major areas of uncertainty are the lack of adequate human exposure data, the extremely short duration of experimental exposures, the lack of reproductive and developmental toxicity studies, and the lack of observation of a NOAEL.

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CHRONIC TOXICITY SUMMARY

PHOSPHINE

(Hydrogen phosphide; phosphorus trihydride; Celphos; Phostoxin)

CAS Registry Number: 7803-51-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.3 μg/m^3; 0.005 ppb** (U.S. EPA RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC
Critical effect(s)	Decreased body weight gain in mice
Hazard index target(s)	Respiratory system; alimentory system; nervous system

II. Chemical Property Summary (HSDB, 1995, except as noted)

Molecular formula	PH_3
Molecular weight	34 g/mol
Description	Colorless gas
Vapor pressure	20 atm @ -3°C; 760 mm Hg @ -87.5°C (Weast, 1980)
Solubility	0.26 volumes in water @ 20°C; soluble in alcohol, ether (Sax and Lewis, 1989)
Conversion factor	1.39 μg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Phosphine is primarily used as an agricultural fumigant against insects and is among the most acutely toxic of the fumigant gases (HSDB, 1995). In its use as a fumigant, application of aluminum, magnesium, or zinc phosphide pellets generates phosphine gas upon exposure to moisture. Because of high volatility, phosphine residue dissipates from treated material upon ventilation. Inadequate sealing of materials during the course of treatment can result in unplanned environmental exposure.

Phosphine is also used by the semiconductor industry as a chemical doping agent for electronic components (n-type semiconductors) (HSDB, 1995). Other minor sources/uses of phosphine are in chemical syntheses; specifically, in preparations of phosphonium halides, for polymerization initiation and as condensation catalysts.

IV. Effects of Exposures to Humans

Toxicity among 22 workers intermittently exposed to phosphine levels of 0.17-2.11 ppm in air from fumigation activity ranging from 0.5 to 29 years (mean = 11.1 years) has been reported (Misra *et al.*, 1988). The most frequently reported symptoms include dyspnea (31.8), headache (31.8%), chest tightness (27.3%), cough (18.2%), anorexia and epigastric pain (18.2%), finger paresthesia and numbness (13.6%), and giddiness, numbness and lethargy (13.6%). The subjects were interviewed within one day of fumigation activity and reported symptoms subsided when phosphine was not in use. No change in motor or sensory nerve conduction velocity was found.

A similar spectrum of toxic effects among workers involved in grain storage at a seaboard terminal has been reported (Jones *et al.*, 1964). Among 69 men exposed to breathing zone phosphine levels of 0-35 ppm for as long as 16 hours per day, the authors report symptoms of multiple origins including: gastrointestinal (diarrhea, nausea, epigastric pain, vomiting), cardio-respiratory (chest tightness, dyspnea, pain in chest, palpitations, retrospinal pain), and central nervous (headache, dizziness, staggering gait) systems. Symptoms were reported to appear only at the time of exposure and appeared reversible.

In another report of chronic occupational exposure, authors cited the appearance of chronic bronchitis, anemia, and digestive disorders (Eichler, 1934).

Most literature reports of human toxic health effects of phosphine, however, come from case reports of acute exposures. Some are suggestive of potential chronic toxicity endpoints because of the irreversible nature of the effect. In a case report of phosphine poisoning of 29 people exposed by inhalation on a grain freighter, pathological findings included evidence of urinary tract injury (occult blood), liver damage (bilirubinuria and increased SGPT, GGPT, and LDH), and myocardial damage (increased MB fraction of CPK, abnormal ECG) (Wilson *et al.*, 1980). A two year old child who died as a result of the exposure showed myocardial necrosis with mononuclear infiltrates, pulmonary edema with damaged epithelia, pleural effusion, and an enlarged spleen. Lethal toxicity to a 7-month pregnant 24 year old woman exposed to aluminum phosphide from a nearby grain storage site was described (Garry *et al.*, 1993). There was evidence of severe pulmonary edema, necrosis of individual hepatic cells, and anoxic change in Purkinje cells of the cerebellum. These reported deaths of a small child and a pregnant woman exposed together with individuals who survived exposure to phosphine suggest there may be sensitive human subpopulations. An acute phosphine poisoning by inhalation was described (Schoonbroodt *et al.*, 1992). Findings included mucosal necrosis and cardiac abnormalities (due to hypoxemia). Renal failure (1/16), proteinuria (1/16), and increased blood transaminases (2/16) have resulted from oral exposure to phosphine (Chopra *et al.*, 1986). The multiorgan involvement in toxicity by phosphine suggests it is a broad spectrum toxicant.

V. Effects of Exposures to Animals

A subchronic inhalation toxicity study of phosphine was conducted in Balb-c mice (Barbosa *et al.*, 1994). Twelve animals/sex/dose group were exposed for 6 hours/day, 5 days/week for 13 weeks to 0, 0.3, 1.0 or 4.5 ppm phosphine. Non-cancer toxicity endpoints included weight gain and relative organ weights of kidneys, lungs, liver, heart, brain and spleen. In the highest dose group, itching and scratching of the eyes, feet and tail, and decreased overall activity was observed. No diarrhea, loss of equilibrium, convulsions, seizures, or other neurological disturbances were noted. A dose-dependent decrease in total body weight gain was observed at all exposure levels with a greater effect observed in females ($p<0.0001$). Statistically significant decreases in relative organ weights (kidney, heart, and brain) were observed in males only at the 0.3 ppm exposure level ($p<0.001$). On the other hand, female mice showed increased relative organ weights (lungs, heart, and spleen) predominantly at higher doses (1.0 and 4.5 ppm; $p<0.001$).

A short-term repeated dose experiment was also conducted by this group, exposing 6 mice/sex/group to 5.5 ppm phosphine for 2 weeks (6 hrs/day, 5 days/wk). No statistically significant changes in weight gain were observed at the end of this exposure period.

Another subchronic inhalation toxicity study of phosphine was conducted in which male and female Fischer 344 rats (10/sex/group) were exposed to levels of 0, 0.37, 1.0 and 3.1 ppm phosphine (Newton *et al.*, 1993). Animals were exposed for 6 hours per day, 5 days per week, for 13 weeks. A higher dose group (10 ppm) was terminated prematurely (at 3 days) because of high mortality. A satellite group exposed to 5.1 ppm for 2 weeks was sacrificed after 13 days recovery. Observations of overt toxicity and viability were made at the time of each exposure, body weight and food consumption were monitored weekly, ophthalmic examination was done the day before sacrifice, and hematological and clinical chemistry indices were measured after 4 and 13 weeks. Postmortem examination included gross necropsy, with particular attention to orifices, the cranial cavity, surfaces of the brain and spinal cord, nasal cavity and sinuses, the thoracic, abdominal and pelvic cavities and viscera, and the cervical tissue and organs. Histopathology was performed on 10% buffered formalin-fixed/hematoxylin-eosin-stained tissues which included adrenal gland, aorta, sternum, brain, esophagus, eyes, heart, cecum, colon, duodenum, ileum, jejunum, kidneys, liver, right lung lobes, lymph nodes, mammary gland, larynx, nasal turbinates, nerve, ovaries, pancreas, pituitary, prostate, salivary glands, seminal vesicles, skin, spinal cord, spleen, stomach, testes with epididymes, thymus, thyroid/parathyroid glands, trachea, urinary bladder, uterus, and vagina.

Significant observations after 13 weeks of phosphine exposure include decreased hemoglobin, hematocrit, and erythrocytes in males in the 3.1 ppm dose group. Male rats in the 1 ppm dose group showed decreased weight gain. Increased incidence of small seminal vesicles was noted at 1 and 3.1 ppm, although no histological correlate was observed. Absolute and relative decreases in liver weight were observed in all exposed groups, but there was no evidence that this effect was dose-related. A significant decrease in serum glutamic pyruvic transaminase (SGPT) was observed at 3.1 ppm, although the authors note unusually high control levels. None of these effects were observed after the 4 week recovery period. Other effects of a transient nature noted

during the course of exposure include decreased weight gain in female rats at 1 ppm, decreased food consumption at 0.37 ppm in males and females, and increased blood urea nitrogen (BUN) at 3.1 ppm. Observations in the 10 ppm group sacrificed after 3 days of exposure included decreased erythrocytes, increased alkaline phosphatase, and increased kidney weight with noted coagulative necrosis of the tubular epithelium of the outer cortex.

Newton *et al.*(1993) also examined developmental toxicity, exposing 24 pregnant female CD^R rats per group to 0, 0.03, 0.33, 2.8, 4.9, and 7.0 ppm phosphine. The highest dose group was terminated prematurely because of high mortality, all other animals were sacrificed after 20 days for evaluation of maternal and fetal toxicity. Maternal toxicity endpoints included weight of ovaries and uteri, number of corpora lutea, pregnancy and implantation rate. Fetal toxicity was evaluated by weight, number and location of fetuses and resorptions, visceral malformations and variations, and skeletal changes after alizarin staining. No statistically significant differences from control animals were observed for any parameter at any dose, with the exception of a change in mean number of resorption sites ($p \leq 0.01$), mean resorption/implant ratio ($p \leq 0.05$), and incidence of females with resorption ($p \leq 0.05$), all at 0.03 ppm only. In the absence of this effect at higher dose levels, these observations are not considered useful in establishing a low adverse effect level.

A 35-day phosphine inhalation study was conducted exposing rats continuously to 0, 0.05, 0.2, 1.5 and 8.0 mg/m^3 phosphine (0, 0.036, 0.14, 1.1, and 5.8 ppm) in which hematological endpoints and histopathological changes of the lungs and kidneys were examined (Pazynich *et al.*, 1984). Observations include a statistically significant change in erythrocytes (increase followed by a decrease at day 35) and decreased hemoglobin at the 0.05 and 0.2 mg/m^3 dose levels, although the 1.5 mg/m^3 dose group did not show this change. Other significant changes noted in the lowest dose group include decreased peroxidase activity after 35 days exposure, decreased sulfhydryl group content in blood after 27 days, and decreased phagocytotic index after 21 days. Some histological changes were noted in the lungs, kidneys, and to a lesser extent, the liver, particularly in the higher dose groups, although the exact nature of the degenerative change is not well described. Unclear dose-response relationships and temporal aspects of the endpoints also make establishment of a low adverse effect level unreliable.

Rats were exposed to 20 ppm phosphine for 14 days (4 hours/day) (Waritz and Brown, 1975). Animals were monitored for weight gain and organs/tissues fixed in Bouin's solution and stained with trichrome were examined histopathologically. There were no reported histopathological effects, although there was slightly reduced weight gain in exposed animals.

VI. Derivation of U.S. EPA Reference Concentration

Study	Barbosa *et al.*, 1994
Study population	Mice (12 animals/sex/group)
Exposure method	Discontinuous inhalation exposure (0, 0.3, 1, or 4.5 ppm)
Critical effects	Decrease in body weight gain
LOAEL	4.5 ppm
NOAEL	1.0 ppm
Exposure continuity	6 hr/day, 5 days/ week
Average experimental exposure	0.18 ppm for NOAEL group
Human equivalent concentration	0.18 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Exposure duration	13 weeks
LOAEL uncertainty factor	1
Subchronic uncertainty factor	10
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Modifying factor	3
Cumulative uncertainty factor	1,000
Reference exposure level	0.0002 ppm (0.2 ppb; 0.0003 mg/m^3; 0.3 $\mu g/m^3$)

The lack of adequate data on levels of chronic phosphine exposure to humans precludes development of a REL from human studies. Barbosa *et al.* (1994), present an adequate animal study for the derivation of a chronic REL. The endpoint used in the determination of the REL (total body weight gain) showed a dose-related decrease with phosphine exposure in Balb-c mice. The endpoint chosen from this animal study is consistent with that found by Newton *et al.* (1993), who also noted dose-dependent decreases in body weight gain in Fischer 344 rats after a 13 week exposure regimen (at 1 ppm), and Waritz and Brown (1975), who report slightly decreased weight gain in rats exposed for 14 days (20 ppm). Although body weight changes or changes in food consumption were not addressed in human studies, the scant human data do relate phosphine exposure to a broad spectrum of toxic effects (gastrointestinal, cardio-respiratory, CNS). The decrease in weight gain found in the animal studies and reported changes in some relative organ weights (Barbosa *et al.*, 1994) suggests systemic toxicity.

The strengths of the inhalation REL include the availability of data on multiple inhalation exposure concentrations and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data, the limited nature of the study, and the lack of reproductive and developmental toxicity studies.

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CHRONIC TOXICITY SUMMARY

PHOSPHORIC ACID

(Orthophosphoric acid)

CAS Registry Number: 7664-38-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**10 µg/m^3** (U.S. EPA RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC
Critical effect(s)	Bronchiolar fibrosis of the respiratory tract in rats
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (HSDB, 1995)

Molecular formula	H_3PO_4
Molecular weight	98
Description	Clear syrupy liquid or unstable crystals
Vapor pressure	0.03 mm Hg @ 20°C
Solubility	Very soluble in hot water; 548 g/100 ml cold water; soluble in alcohol
Conversion factor	4.0 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Phosphoric acid has varied uses (HSDB, 1995). In manufacturing, it is a chemical intermediate or reagent in the production of numerous phosphate fertilizers, agricultural feeds, waxes, polishes, soaps, and detergents. It is added to foods as a preservative, acidifying agent, flavor enhancer, and clarifying agent. Phosphoric acid is also used in processes such as the coagulation of rubber latex, electropolishing, soil stabilization, and as a catalyst in the production of propylene and butene polymers, ethylbenzene, and cumene. By far, largest use of phosphoric acid comes in the production of fertilizers (>75%).

Airborne phosphoric acid can be produced by the hydrolysis of phosphorus oxides generated from either the spontaneous ignition of white phosphorus in air or the combustion of red phosphorus (Burton *et al.*, 1982; US Department of Defense (US DOD), 1981).

IV. Effects of Human Exposures

The toxic effects to 48 workers exposed (28 unexposed control workers) to oxidation products of phosphorus during the course of phosphorus production were reported (Hughes *et al.*, 1962). Exposure duration ranged from 1 to 17 years. No differences were observed between exposed and control workers with respect to leukocyte count (an effect observed in acute intoxications) or hand bone density (an effect observed in experimentally exposed animals (Inuzuka, 1956).

A prospective study of 131 workers exposed to several compounds including phosphoric acid, phosphorus pentoxide, fluorides and coal tar pitch in the air was conducted at an industrial refinery (Dutton *et al.*, 1993). Mean duration of exposure (employment) was 11.4 years and the maximum exposure level measured was 2.23 mg/m^3 (phosphorus pentoxide). Pulmonary function tests were performed annually over a 3 to 7 year period. No significant residual effect was found after adjusting for age and smoking status.

V. Effects of Animal Exposures

Two 13-week inhalation studies of the effects of exposure to the combustion products of 95% red phosphorus and 5% butyl rubber were conducted in male Sprague-Dawley rats, with the first group exposed to 0, 300, 750, or 1200 mg/m^3 combustion products, and the second exposed to 0, 50, 180, or 300 mg/m^3 combustion products (Aranyi *et al.*, 1988a; Aranyi *et al.*, 1988b). Group numbers in the first study were 176, 84, 176, and 176, respectively, and in the second study consisted of 40 animals/group. Animals were exposed for 2¼ hours/day on 4 consecutive days/week. Control animals were exposed to filtered air only. Daily particle measurements showed MMADs of 0.49-0.65 μm and σ_g's of 1.56-1.83. Fractional content of phosphoric acid in the aerosol was 71-79%. Nineteen of the 176 animals in the 1200 mg/m^3 dose group died of treatment related effects. Post-mortem examination of animals that died during the course of the study showed damage to the laryngeal mucosa was probably contributory to mortality. The two highest dose groups in the first study also showed decreased weight gain. Twelve animals from each dose group in the first study were examine histologically and neurobehavioral studies were conducted on other animals. Half the animals in the second study were examined strictly for toxic effects on the respiratory tract, with examination of the trachea, 2 sections of the nasal turbinates, and 5 lobes of the lung. Surviving animals in the high-dose study were observed to have moderate to severe fibrosis of the terminal bronchioles, with minimal severity of this effect in the animals in the low-dose study. The reported incidence of this lesion was 9/20 at 300 mg/m^3, 4/20 at 180 mg/m^3, and 0/20 at 50 mg/m^3. Little to no involvement of pulmonary tissue was observed.

The effects of acid aerosols (particularly sulfuric and phosphoric acid were studied (U.S. EPA, 1989). One finding was that the respiratory tract was the primary target of toxicity resulting from the irritational effect of the acid on the tissues of the larynx and trachea. The nature of the effect was dependent upon the aerosol particle size, duration of exposure, and the hygroscopic character of the acid.

Sprague-Dawley rats were exposed to the smoke and combustion products of white phosphorus in felt pellets at 192.5 (18 animals/sex), 589 (24 animals/sex), or 1161 mg/m^3 (34 males, 43 females) (phosphoric acid equivalents) for 15 minutes/day, 5 days/week, for 13 weeks (US Department of Defense (US DOD), 1981). Control animals numbering half the size of the treated groups were exposed to air only. Groups of animals were sacrificed at 6 and 13 weeks, and 4 weeks post-exposure. Endpoints examined included: hematology, clinical chemistry, gross- and histo-pathology, ECG, pulmonary function, and behavior. Of the animals in the highest dose group, 56% died as a result of exposure, with the only other death occurring in the control group. Findings were restricted to effects on the respiratory system, with tracheitis and laryngitis incidences of 28/31, 32/47, and 2/35 among surviving animals in the three decreasing dose groups. In the post-exposure examination, bronchiolitis occurred with a frequency of 6/16, 5/24, and 0/12 in the three decreasing dose groups.

The toxicity of the combustion products of 95% amorphous red phosphorus and 5% polyvinyl butyral BL18 to female Wistar rats, Porton-strain mice, and guinea pigs was reported (Marrs *et al.*, 1989). Rats (50/group), mice (100/group), and guinea pigs (42-48/group) were exposed to concentrations of 0, 16, or 128 mg/m^3 for 1 hour/day, 5 days/week for 36 weeks (mice) or 40 weeks (rats and guinea pigs), with an examination conducted at 19 months or when animals appeared unhealthy. All groups, including controls, showed high mortality. Mice showed accumulation of alveolar macrophages with an incidence of 2/41, 9/37, and 9/22 in the control, low-, and high-dose groups, respectively. Guinea pigs were noted to appear particularly intolerant to the effects of the smoke.

Female rabbits and rats (10/group) were examined for acute toxic effects of smoke generated by the combustion of either 95% red phosphorus / 5% butyl rubber (Smoke I) or 97% red phosphorus / 3% butadiene styrene (Smoke II) (Marrs, 1984). Animals were exposed for 30 minutes and examined one and 14 days later. Smoke I produced inflammation of the larynx and trachea in rats at 1 day with some inflammation still observed at 14 days. Tracheal inflammation was also reported in rabbits exposed to Smoke I. Four of the rats exposed to Smoke II died within the first day, with severe pulmonary congestion observed in the animals.

One hour exposure to the combustion products of 95% red phosphorus / 5% butyl rubber (plus 1% mineral oil) produced epiglottal deformation, laryngeal edema, and laryngeal and tracheal lesions in rats (Burton *et al.*, 1982). Four hour exposure produced more severe effects of a similar nature plus some hemorrhaging.

Rats (number unspecified) exposed to 150-160 mg/m^3 elemental phosphorus for 30 minutes/day for 60 days were examined for toxic effects (Inuzuka, 1956). Limb bone abnormalities were noted effects and included delayed ossification, widening of the epiphysis, and abnormal axial development.

Two studies have addressed the reproductive and developmental toxicity from exposure to the combustion products of white phosphorus and felt for 15 minutes/day during gestational days 6-15 in rats (24/group) (US Department of Defense (US DOD), 1981; US Department of Defense

(US DOD), 1982). Fetal effects reported included increased incidence of some visceral variations and hypoplasia of the xiphoid process although data were reported incompletely. Another study exposed dams 3 weeks prior to mating, throughout gestation, and through lactation and males for 10 weeks prior to and during mating showed decreased pup body weight, 24-hour and 21-day survival, and lactation. An oral study in which elemental phosphorus was administered to male and female rats by gavage in corn oil showed no statistically significant effects (Condray, 1985).

VI. Derivation of the U.S. EPA RfC

Study	Aranyi *et al.*, 1988a
Study population	Male Sprague-Dawley rats
Exposure method	Discontinuous whole body inhalation
Critical effects	Bronchiolar fibrosis of the respiratory tract
LOAEL	180 mg/m^3
NOAEL	50 mg/m^3
BMC10	100 mg/m^3
Exposure continuity	2¼ hours/day, 4 days/week
Exposure duration	13 weeks
Average experimental exposure	2.7 mg/m^3 for NOAEL group (estimated as 5.4 mg/m^3 at BMC_{10})
Human equivalent concentration	3.3 mg/m^3 at BMC_{10} (particle with respiratory efffects, RDDR = 0.63)
LOAEL uncertainty factor	1 (BMC_{10} assumed to be similar to NOAEL)
Subchronic uncertainty factor	10
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Reference exposure level	0.01 mg/m^3 (10 $\mu g/m^3$)

The U.S. EPA has used a benchmark dose methodology for the derivation of the reference concentration (RfC) for phosphoric acid from the toxicity data in the Aranyi *et al.* (1988) study (U.S. EPA, 1995). The RfC is restricted to "aerosols of phosphoric acid and phosphorus oxidation products and does not apply to elemental phosphorus or other forms of phosphorus, such as phosphorus salts". The Aranyi *et al.* (1988a) study represents the most adequate study for the quantitative evaluation of the toxicity of phosphoric acid. It was conducted with a large number of animals with multiple doses, produced good dose-response data, and examined likely targets of toxicity (respiratory system) of smoke generated from the combustion of phosphorus and butyl rubber. Uncertainties associated with these data, however, include that (1) the study used combustion products of phosphorus rather than phosphoric acid itself, (2) the total exposure time was relatively short and discontinuous over the duration of the experiment, and (3) only one species/strain/sex was studied.

The U.S. EPA, using the Weibull model, estimated the lower 95% confidence level bound on the maximum likelihood estimate (MLE = 150 mg/m^3) resulting in 10% incidence of lesions in the tracheobronchiolar region to be 100 mg/m^3 (the BMC10). The U.S. EPA considered 10% incidence level to be a correlate to the NOAEL, based on a precedent in the analysis of data with developmental toxicity endpoints (Allen *et al.*, 1994; Faustman *et al.*, 1994). After correction for exposure continuity, a regional deposited dose ratio (RDDR) for the tracheobronchial region of 0.64 was applied given the availability of data concerning the growth and deposition of phosphoric acid aerosol particles in humans and similarities in the effects of phosphoric and better-characterized sulfuric acid aerosols. Key assumptions in the generation of this factor include: (1) the lowest σ_g of 1.56 μm cited in the study was used in the calculation, (2) geometric rather than aerodynamic diameter approximations were used, (3) particles of this size reach the deposition / lesion site (bronchioles), (4) these hygroscopic particles become more uniform with growth, and (5) particle growth is similar in humans and rodents. An uncertainty factor of 10 was applied because of the subchronic duration of the study. A factor of 3 was applied for interspecies extrapolation in light of the fact that some correction for human equivalency was made with the RDDR. Finally, a factor of 10 was applied for protection against potentially sensitive human subpopulations. The resulting chronic REL for phosphoric acid is 0.01 mg/m^3.

The strengths of the inhalation REL include the availability of subchronic inhalation exposure data from a well-conducted study with histopathological analysis and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data, the lack of chronic inhalation exposure studies and the discontinuous nature of exposures (only 2 1/4 hours per day).

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CHRONIC TOXICITY SUMMARY

PHOSPHORUS

(yellow phosphorus; white phosphorus; black phosphorus; red phosphorus)

CAS Registry Number: 7723-14-0

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.07 µg/m^3**
Oral reference exposure level	**0.02 µg/kg-day** (U.S. EPA RfD) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfD
Critical effect(s)	Reproductive toxicity in rats
Hazard index target(s)	Reproductive system

II. Chemical Property Summary (HSDB, 1995)

Molecular formula	P_4
Molecular weight	123.92 g/mol
Description	Colorless, yellow or white, waxy or crystalline solid (yellow or white phosphorus)
Vapor pressure	0.026 mm Hg @ 20°C
Solubility	White: sol. in 300000 parts H_2O, 1 g sol. in 400 ml alcohol, 102 ml ether, 40 ml chloroform, 35 ml benzene, 0.8 ml CS_2, 80 ml olive oil, 60 ml turpentine, 100 ml almond oil
Conversion factor	5.07 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources (HSDB, 1995)

White phosphorus was formerly used in the manufacture of rat and cockroach poisons (by grinding with water and flour) and has current use in gas analysis. Red phosphorus is produced from white phosphorus by heating. Red phosphorus has many uses including the manufacture of matches, fertilizers, pesticides, incendiary shells, fireworks, screening smokes, and tracer bullets. Aqueous red phosphorus is used to remove nitrogen dioxide from flue gases. Phosphorus is also a chemical intermediate in the production of phosphoric acid (its primary use), phosphoric anhydride, phosphine, phosphorus pentachloride, phosphorus trichloride, and calcium metaphosphate.

IV. Effects of Human Exposure

"Phossy jaw" is a well-known manifestation of chronic phosphorus exposure observed in occupationally exposed workers. Progressive symptoms begin as a local inflammation or irritation and proceed to swelling, ulceration, and destruction of the jawbone with perforation to the sinus or nasal cavities and externally to the cheek (Gordon, 1992; Davidson *et al.*, 1987). Exposure levels were not available in the studies.

Workers occupationally exposed to phosphorus for a long period in the production of products such as firecrackers, matches, rat poison, and white phosphorus itself were reported to develop "phossy jaw" (Davidson *et al.*, 1987). Severe effects included brittle bones, loss of appetite, diarrhea, emaciation, degeneration of the abdominal organs, and death. No adverse hematological or skeletal effects were reported among 48 phosphorus workers (Hughes *et al.*, 1962).

V. Effects of Animal Exposure

The principal target organ of white phosphorus toxicity in experimental animals is the skeletal system. Hepatic and reproductive effects have also been reported. Rabbits were administered 0.3 mg/kg-day white phosphorus in tablets for 117-133 days (Adams and Sarnat, 1940). Decreased weight gain and decreased average daily growth of the tibial diaphysis were reported. In this study, white rabbits (15-17/group) were also administered 0.01% white phosphorus in cod liver oil in feed for 22-57 days. Skeletal changes observed include retardation in the normal tubulation process, narrowing of the epiphyseal cartilage plate, reduction in the number of cartilage cells per column, increased density in the metaphyseal zone, and in some cases, replacement of the hematopoietic marrow of the bone with loose fibrous tissue.

In a series of unpublished studies, rats were exposed to 20 ppm phosphorus vapors for 7 hours/day, 5 days/week (TVA, 1953; as reported in ACGIH, 1992). This exposure regimen produced respiratory irritation and resulted in a high level of mortality from bronchopneumonia and edema. The growth of animals exposed to 13-16 ppm phosphorus for 7 hours/day, 5 days/week for 4 months was not significantly different from concurrent controls (TVA, 1947), however, bone changes were observed in the exposed animals (TVA, 1950).

Seven Sprague-Dawley rats were exposed by inhalation to an aerosol of fresh red phosphorus for four one hour periods at concentrations ranging from 3.2 to 8.5 mg/l and one 4-hour period at 1.5 mg/l. Animals died from 1 to 11 days after exposure. Ulceration and edema of the larynx and epiglottis were observed at the lower doses. At the higher doses, pulmonary edema and hemorrhage were observed (Burton *et al.*, 1982).

Daily exposure by inhalation for 30 minutes to 150-160 mg/m^3 phosphorus vapor was reported to lead to decreased hemoglobin and erythrocyte count (ACGIH, 1971; HSDB, 1995).

In a chronic oral study, male and female rats were treated by oral administration of white phosphorus in peanut oil at doses of 0, 0.2, 0.4, 0.8, or 1.6 mg/kg-day for life (Fleming *et al.*, 1942). The report indicated that growth retardation and decreased food consumption occurred in treated animals along with changes in the bone (thickening of the epiphyseal line and extension of the trabeculae into the shaft). No other effects were observed.

In a subchronic study, rabbits and guinea pigs were administered 0.66-1.0 mg/kg-day white phosphorus in the oil of sweet almonds for up to 3 months (Mallory, 1933). Cirrhosis of the liver was observed in both species. Pre-cirrhotic liver lesions were reported in guinea pigs administered a 0.1% solution of white phosphorus in olive oil by gavage at doses of 0.75 mg/kg for 4 days/week or 1.5 mg/kg for 2 days/week (Ashburn *et al.*, 1948). Total exposure duration was 35 weeks.

Female albino rats (6-10/group) were fed diets containing white phosphorus such that the median dose was 0.0032, 0.018, or 0.072 mg/kg-day for 22 weeks (Sollmann, 1925). Ten male rats were also fed at a dose rate of 0.0027 mg/kg-day for 25 weeks. No concurrent controls were included in the study. Mortality ranged from 30 to 50% in treated female groups and was 10% among the male rats. Weight loss was reported in all treated females, although this effect was only temporary in the low-dose group.

Male (15/group) and female (30/group) rats were administered 0, 0.005, 0.015, or 0.075 mg/kg-day yellow phosphorus in corn oil by gavage beginning 80 days prior to mating and continuing through weaning of two complete reproductive cycles (Condray, 1985). The high dose females exhibited a high rate of mortality and hair loss on the forelimbs while high dose males had decreased mean body weight at 15 weeks of treatment. No other adverse effects were observed indicating a NOAEL for reproductive effects of white phosphorus in rats of 0.015 mg/kg-day and a LOAEL of 0.075 mg/kg-day.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Condray, 1985
Study population	Rats
Exposure method	Oral gavage
Critical effects	Decreased mean body weight; increased parturition mortality; forelimb hair loss
LOAEL	0.075 mg/kg-day
NOAEL	0.015 mg/kg-day
Exposure continuity	1
Exposure duration	80 days plus two complete reproductive cycles
Average experimental exposure	0.015 mg/kg-day
LOAEL uncertainty factor	1
Subchronic uncertainty factor;	3
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Modifying factor	3 (incomplete developmental/reproductive toxicity data)
Cumulative uncertainty factor	1,000
Oral reference exposure level	0.00002 mg/kg-day (U.S. EPA RfD)
Inhalation extrapolation factor	3,500 $\mu g/m^3$ per mg/kg-day
Inhalation reference exposure level	0.00007 mg/m^3, 0.07 $\mu g/m^3$; 0.00001 ppm; 0.01 ppb)

There are no data available relating inhalation exposure in humans to adverse effects suitable for the development of a chronic REL. Furthermore, the available inhalation data from experimental animals are of inadequate quality to reliably relate specific exposure levels to toxic effects. There are, however, important qualitative similarities between the adverse effects associated with inhalation and oral exposure to phosphorus. Specifically, exposure by both routes results in toxic effects to the skeletal system. Since adverse effects from systemic exposure to phosphorus at other sites cannot be ruled out, and information related to such effects is not available in inhalation studies, the chronic REL is based on the most sensitive and well-reported of the effects observed in experimental animals. For these reasons, the chronic REL for white phosphorus has been adopted based upon the oral reference dose (RfD) developed by the U.S. EPA (U.S. EPA , 1990).

The strengths of the inhalation REL include the availability of subchronic controlled exposure data and the observation of a NOAEL. Major areas of uncertainty are the lack of adequate human exposure data, the lack of inhalation exposure studies, and the lack of reproductive and developmental toxicity studies.

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CHRONIC TOXICITY SUMMARY

PHTHALIC ANHYDRIDE

(1,3-Isobenzofurandione; phthalic acid anhydride)

CAS Registry Number: 85-44-9

I. Chronic Toxicity Summary

Inhalation reference exposure level	**10 µg/m^3**
Critical effect(s)	Eye and respiratory irritation, asthma, and bronchitis in occupationally exposed workers
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (from HSDB, 1995)

Molecular formula	$C_8H_4O_3$
Molecular weight	148.11 g/mol
Description	White or pale yellow crystals
Vapor pressure	5.14×10^{-4} mm Hg @ 25°C; 1 mm Hg @ 96.5°C
Solubility	Soluble in 162 parts water, 125 parts carbon disulfide; soluble in hot benzene
Conversion factor	6.1 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

The primary use of phthalic anhydride (PA) is as a chemical intermediate in the production of plastics from vinyl chloride. Phthalate esters, which function as plasticizers, are derived from phthalic anhydride. Phthalic anhydride has another major use in the production of polyester resins and other minor uses in the production of alkyd resins used in paints and lacquers, certain dyes (anthraquinone, phthalein, rhodamine, phthalocyanine, fluorescein, and xanthene dyes), insect repellents, and urethane polyester polyols. It has also been used as a rubber scorch inhibitor and retarder (HSDB, 1995; National Cancer Institute (NCI), 1979).

IV. Effects of Human Exposure

Symptoms in workers exposed to phthalic anhydride by inhalation in two plants (A and B) manufacturing alkyd and unsaturated polyester resins were studied (Nielsen *et al.*, 1988). Two groups of exposed workers were identified in each plant. One group worked directly loading the reactors from bags of phthalic anhydride ("heavy" exposure - 35 workers) and the other group

was involved with "other work" which led to "low" exposure (25 workers). Mean employment times for the "heavy" and "low" exposure groups were 13.3 and 11.9 years, respectively. Time-weighted average air concentrations for workers from the loading of PA was 6.1 (range: 1.8-14.9) and 6.8 mg PA/m^3 (range: 1.5-17.4) in plants A and B, respectively. Similar exposure levels in both plants led to pooling of data. The exposure duration of the "heavy" group was estimated at approximately 30 minutes two times a day, corresponding to the time of loading and resulted in a full-day time weighted exposure estimate of 0.4 mg PA/m^3. For those engaged in "other work" exposure levels were estimated at < 0.1 mg PA/m^3 (the limit of detection). Other chemicals in use in smaller amounts included maleic anhydride, isophthalic anhydride, and trimellitic anhydride. Comparison of symptom incidence between the "heavy" and "low" exposure groups included conjunctivitis (46% vs. 20%), rhinitis (40% vs. 20%), rhinoconjunctivitis (17% vs. 12%), asthma (17% vs. 0%), and chronic bronchitis (17% vs. 4%). Serum antibodies were measured in both groups of workers and compared to 22 nonexposed workers (employed at a food processing factory). The only significantly changed level was an increase in specific IgG in the "heavy" exposure group. A correlation was also noted between specific IgG level and exposure level, although not all individuals with elevated specific IgG reported symptoms.

In a study conducted at another plant manufacturing alkyd and/or unsaturated polyester resins, serum immunoglobulins and lung function were examined in 23 workers exposed to phthalic anhydride and 18 control subjects (Nielsen *et al.*, 1991). Estimated exposure levels were 6.6 mg PA/m^3 (range: 1.5-17) (Nielsen *et al.*, 1988). Workers were examined for sensitization to PA and other allergens and possible development of small airways disease. Among the exposed workers, there was significantly increased reporting of conjunctivitis and rhinoconjunctivitis. One worker showed an asthmatic response to anhydrides. No significant differences in lung-function tests were observed between exposed and unexposed groups.

Symptoms in workers occupationally exposed to PA during the course of producing alkyd and/or polyunsaturated polyester resins were described (Wernfors *et al.*, 1986). Exposure estimates of breathing zone PA levels ranged from 3 to 13 mg/m^3 for workers engaged directly with the handling of PA. In other areas the estimated level was <0.3 mg/m^3. The study examined 48 workers who were employed at the time of the study and 70 former employees who responded to a survey of symptoms related to exposure. No unexposed control group was included in the study. Workers who were employed for at least two months reported symptoms of rhinitis (28%), chronic bronchitis (11%), and asthma (28%). Among a subset of 11 workers with asthma, 3 had positive skin tests for PA sensitivity. Bronchial provocation tests with 6 or 0.5 mg/m^3 PA for 5 or 10 minutes were positive in 2 workers.

V. Effects of Animal Exposure

Male albino rats (6/treatment group) were exposed to phthalic anhydride vapors at 0, 0.02, 0.2, and 1 mg/m^3 continuously for 45 days (Protsenko, 1970). After a two week recovery period the testes were examined for spermatozoa motility time as well as for ascorbic acid, dehydroascorbic acid, and nucleic acid content. Motility time was defined as the time it took for spermatozoa to cease motion completely under microscopic examination. Spermatozoa motility time was

decreased ~50% in the 1 mg/m^3 dose group and ~25% in the 0.2 mg/m^3 dose group. Significant decreases in ascorbic acid and dehydroascorbic acid levels were found in animals exposed to 0.2 and 1.0 mg/m^3 phthalic anhydride, and dehydroascorbic acid levels were decreased in the 0.02 mg/m^3 dose group. At 1 mg/m^3, RNA levels and combined RNA and DNA levels were significantly increased over controls. No significant changes were observed in the 0.02 mg/m^3 dose group.

Five and six female Hartley guinea pigs were exposed to 0.05-0.2 mg/m^3 and 0.6-6 mg/m^3 phthalic anhydride dust, respectively, for 3 hours/day for 5 consecutive days (Sarlo and Clark, 1992). Exposures were expressed as ranges due to difficulty in regulating dust levels in the chambers. Sampling of dust showed particles were 65-80% < 10μm diameter and had a mean mass diameter of 5.8-9.8 μm. Eight control animals were exposed to filtered air only. Two weeks after the last exposure, animals were challenged for 30 minutes with aerosolized PA-guinea pig serum albumin conjugate. All animals in the "high" dose group showed immediate bronchoconstriction and transiently increased respiratory rate. Animals in this dose group also showed elevated IgG antibody titers. No detectable increase in antibody levels was found in the "low" dose group.

Type I hypersensitivity was examined in female Hartley guinea pigs exposed to phthalic anhydride dust (Sarlo *et al.*, 1994). Two groups of 8 animals were exposed to 0.5 or 1.0 mg/m^3, and two groups of 16 animals were exposed to 0 (filtered air only) or 5.0 mg/m^3 phthalic anhydride dust (respirable size - 5 μm) in stainless steel chambers for 3 hours/day for 5 consecutive days. Groups of 8 animals from the control and 5 mg/m^3 groups were challenged after a two week recovery period for 30 minutes with 5.0 mg/m^3 phthalic anhydride dust. Respiratory data were collected using a plethysmograph from 30 minutes before the exposure to 60 minutes after the exposure. No significant difference (defined as a change of 3 standard deviations from the same parameter in the control animals) in respiration rate or plethysmograph pressures was found between the exposed and unexposed animals. Eight animals in each of the four exposure groups were also challenged after two weeks of recovery with 2.0 mg/m^3 aerosolized PA-guinea pig serum albumin (GPSA) conjugate as described above. Respiratory rate was increased in 4/8 of the high-dose group animals and 1/8 of the low-dose animals. Plethysmograph pressures were increased in 3/8 animals in the high-dose group and one animal each in the low- and mid-dose groups. Serum IgG antibodies to PA-GPSA were elevated in all exposed animal groups and the effect showed a dose-response. Passive cutaneous anaphylaxis testing for anti-phthalic anhydride-GPSA IgG1a immunoglobulins showed positive results for 3/8, 1/8, and 5/8 animals in the 0.5, 1.0, and 5.0 mg/m^3 dose groups, respectively. Results in control animals were not described. Three of eight animals in the highest dose group had >189 hemorrhagic foci in their lungs. No control animals had more than 2 such foci. No foci were observed in albumin conjugate challenged animals. Serum IgG titer correlated with the presence of these foci.

A study was conducted by Slavgorodskiy (1969) concerning the toxicity of phthalic anhydride to animals from inhalation exposure. Sixty white male rats (group distribution not stated, but presumed to be 15 animals/treatment group) were exposed in 100 l chambers to 0, 0.18, 0.54, and 1.52 mg PA/m^3 aerosol continuously for 70 days. General condition and behavior, body weight,

motor chronaxy of flexor and extensor muscles (every 10 days), cholinesterase activity (every two weeks), and hematological parameters were monitored during the course of the study. No changes in body weight or behavior were observed in the treated animals. In animals in the high-dose group, the chronaxy ratio of flexors and extensors differed from the controls beginning on day 31 of exposure and continued until two weeks after exposure ceased. Significantly decreased whole blood cholinesterase activity occurred in the high- and mid-dose groups, with the change occurring after 42 days of exposure. An increase in thrombocyte count occurred in the high- and mid-dose groups after 70 days of exposure, but returned to normal during the two week recovery period.

A chronic feeding study was conducted with phthalic anhydride in rats and mice to evaluate the carcinogenicity of the compound (National Cancer Institute (NCI), 1979). F344 rats (50/sex/dose group plus 20/sex control animals) were treated with diet containing 0, 7500, or 15000 ppm phthalic anhydride for 105 weeks (which corresponds to ~ 0, 300, and 600 mg/kg-day, assuming food consumption is 4% body weight/day). Animals were monitored for changes in body weight, survival, and upon death or the end of the study were examined histopathologically. The only group showing significantly lower body weights were male rats in the high-dose group after week 13. No significant change in mortality was observed. Adverse non-cancer effects observed in the dosed groups, but not in the control animals, included “arched back, rough hair coat, ulceration, and corneal opacity”, however, incidences were described as “low”. No significant histopathological effects were found to be associated with exposure to phthalic anhydride. $B6C3F_1$ mice (50/sex/dose group plus 20/sex control animals) were initially treated with diet containing 0, 25000, or 50000 ppm phthalic anhydride (~ 0, 3000, and 6000 mg/kg-day, assuming food consumption is 12% body weight/day). Because of excessive weight loss after week 32, dose levels were reduced during the course of the study such that the time-weighted average dose for males was 16,346 and 32,692 ppm and for females was 12,019 and 24,038 ppm phthalic anhydride. Evaluation of toxicity was conducted at 104 weeks as with the rats. Mean body weight change was reduced in male and female mice in a dose-related manner. No other significant treatment-related adverse effects were observed in the mice.

Pregnant female CD-1 mice (10/dose group) were treated intraperitoneally with phthalic anhydride in 0.5%(w/v) carboxymethyl cellulose solution on gestational days 8-10 (Fabro *et al.*, 1982). Dosing was variable, beginning within the 95% confidence limits of the LD_{01} and progressed geometrically downward until no effect was observed. Animals were sacrificed on Day 18 and examined for teratogenic effects including fetal viability and number, resorption, and gross malformations. The 95% lower confidence limit on the dose producing teratogenicity in 5% and 50% of animals were 0.40 and 1.37 mmol/kg-day (59 and 203 mg/kg-day), respectively.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Neilsen *et al.* (1988; 1991)
Study population	23 Occupationally-exposed workers
Exposure method	Discontinuous occupational inhalation exposures
Critical effects	Increased incidence of conjunctivitis, rhinitis, asthma, and chronic bronchitis
LOAEL	6.5 mg/m^3
NOAEL	Not observed
Exposure continuity	8 hours/day, 5 days/week
Exposure duration	Mean of 13.3 years
Average experimental exposure	1.5 mg/m^3 for LOAEL group ($6.6\ mg/m^3 \times (8/24) \times (5/7)$)
LOAEL uncertainty factor	10
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.01 mg/m^3 (10 $\mu g/m^3$)

Adverse effects were demonstrated to occur in humans occupationally exposed to phthalic anhydride in the workplace over long periods of time (Nielsen *et al.*, 1988). The symptoms reported primarily affected the respiratory system, with increased incidence of rhinitis, rhinoconjunctivitis, asthma, and chronic bronchitis. Conjunctivitis was also reported in exposed workers. Specific anti-PA IgG was significantly elevated compared to a non-exposed group. Increased incidences of rhinoconjunctivitis, conjunctivitis, or chronic bronchitis have also been reported in workers exposed to similar levels of PA dust (Nielsen *et al.*, 1991; Wernfors *et al.*, 1986). In these reports, adverse effects were clearly observed at the exposure level reported (6.5 mg PA/m^3; full-day time weighted exposure of 0.4 mg PA/m^3). Although symptoms were reported by Nielsen (1988) in the lower exposure level group, their level of significance is not clear since a true control group (unexposed workers) was not included in the symptomatology section of the study. The low exposure group's level of exposure was less than the detection limit for phthalic anhydride cited in the study, and this group was considered as a control group.

The strengths of the inhalation REL include the use of human exposure data from workers exposed over a period of years. Major areas of uncertainty are the uncertainty in estimating exposure and the potential variability in exposure concentration, the potential low exposures of the group considered as controls, potential confounding by exposures to other chemicals, the limited nature of the study, the lack of reproductive and developmental toxicity studies, and the lack of observation of a NOAEL. Another area of uncertainty is the apparent 10-fold greater sensitivity to bronchoconstriction from PA exposure in guinea pigs (a model for human asthmatics) in comparison to occupationally-exposed workers.

The study in rats by Protsenko (1970) identified a LOAEL of 0.2 mg/m^3 for decreased sperm motility. However, this result from 1970 has not been verified or further explored in modern toxicological or epidemiological studies. The small sample size of 6/group further weakens confidence in this result. Therefore, the study in workers by Nielson *et al.* (1988, 1991) was chosen as the basis for the REL for PA.

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CHRONIC TOXICITY SUMMARY

PROPYLENE

(1-propene; 1-propylene; propene; methylethene; methylethylene)

CAS Registry Number: 115-07-1

I. Chronic Toxicity Summary

Inhalation reference exposure level	**3,000 μg/m^3**
Critical effect(s)	Squamous metaplasia [males and females], epithelial hyperplasia [females only], and inflammation [males only] of nasal cavity) in Fisher 344/N rats
Hazard index target(s)	Respiratory system

II. Chemical and Physical Properties (HSDB, 1995)

Molecular formula:	C_3H_6
Molecular Weight:	42.08
Description:	Colorless gas; practically odorless.
Vapor Pressure:	8690 mm Hg at 25°C
Solubility:	Soluble in alcohol and ether.
Conversion factor:	1.72 μg/m^3 per ppb at 25°C

III. Major Uses and Sources (HSDB 1995)

Propylene is produced primarily as a by-product of petroleum refining and of ethylene production by steam cracking of hydrocarbon feedstocks. Propylene is a major chemical intermediate. The most important derivatives of chemical and polymer grade propylene are polypropylene, acrylonitrile, propylene oxide, isopropanol and cumene. Use of polypropylene in plastics (injection moulding) and fibers (carpets) accounts for over one-third of U.S. consumption. It is also used in the production of synthetic rubber and as a propellant or component in aerosols. In 1994, propylene was ranked seventh among the top 50 chemicals produced domestically (C&EN, 1995). In the environment, propylene occurs as a natural product from vegetation. It is also a product of combustion of organic matter (biomass burning, motor vehicle exhausts and tobacco smoke) and is released during production and use. The most probable route of exposure to humans is by inhalation. Propylene has been detected in the atmosphere over both metropolitan (2.6 to 23.3 ppb) and rural (0.007 to 4.8 ppb) areas (Cox *et al.*, 1976; Leonard *et al.*, 1976).

IV. Effects of Human Exposures

No data were available on the absorption, distribution or excretion of propylene in humans. However, hemoglobin (Hb) adducts of the metabolite intermediate propylene oxide have been used to monitor the internal dose of propylene (Tornqvist and Ehrenberg, 1990). The background level of the 2-hydroxylpropyl adduct to the N-terminal valine of hemoglobin was found to be about 2 pmol/g Hb. This was estimated to be equivalent to smoking 10 cigarettes per day; cigarette smoking being a source of propylene. Occupational exposure to propylene at 1 ppm (1.72 mg/m^3) was assumed to be associated with an increment of 5 pmol/g Hb (Kautiainen and Tornqvist, 1991).

No data were available on the chronic effects of propylene in humans.

V. Effects of Animal Exposures

In rats and mice, most propylene inhaled into the lungs is exhaled again and does not reach the blood to become systemically available (Golka *et al.*, 1989; Svensson and Osterman-Golkar, 1984). Once absorbed, a major route of metabolism for propylene is through the cytochrome P-450 system to propylene oxide, a known carcinogen in experimental animals. Cytochrome P-450 enzymes in both the liver and nasal epithelium (Maples and Dahl, 1991) can convert propylene to its toxic metabolite. However, in rats propylene metabolism becomes increasingly saturated at concentrations above 50 ppm (86 mg/m^3) in the atmosphere (Golka *et al.*, 1989), limiting the amount of propylene oxide produced. Therefore, the amount of absorbed propylene may not reach high enough levels in classical long-term inhalation studies (Quest *et al.*, 1984) to show positive carcinogenic or serious chronic effects.

The only chronic toxicity investigation found for propylene was a comprehensive 2-year study in F344/N rats and $B6C3F_1$ mice (Quest *et al.*, 1984; NTP, 1985). Groups of 50 rats and 50 mice of each sex were exposed to concentrations of 0, 5000 and 10,000 ppm (mean daily concentrations were 4985 and 9891 ppm, respectively, for the rat study; and 4999 and 9957 ppm, respectively, for the mouse study), 6 hr/day, 5 dats/week, for 103 weeks. In exposed rats, treatment-related chronic effects were observed in the nasal cavity. In female rats, epithelial hyperplasia occurred in the high dose group and squamous metaplasia occurred in both dosage groups. In male rats, squamous metaplasia was seen only in the low dose group, but both dosage groups had inflammatory changes characterized by an influx of lymphocytes, macrophages and granulocytes into the submucosa and granulocytes into the lumen. Nasal lesions were not observed in mice. The inflammatory lesions were more severe in the high dose group. Very mild focal inflammation was observed in the kidneys of treated mice but the relationship to propylene exposure was unclear. No other treatment-related effects, including clinical signs, mortality, mean organ and body weights and histopathology, were observed.

In a long-term carcinogenicity study, Sprague-Dawley rats and Swiss mice (100-120 animals/group/sex) were exposed by inhalation to 0, 200, 1000 and 5000 ppm propylene 7 hr/day, 5 days/week, for 104 weeks (rats) or 78 weeks (mice) (Ciliberti *et al.*, 1988). No body weight differences were observed between treated and control animals of either species.

Mortality was reported to be slightly increased in male rats in the 1000 and 5000 ppm groups and in male mice in the 5000 ppm group, but numerical values of mortality were not presented in the report. Therefore, it is assumed that mortality differences were insignificant. Other possible general body system or nonneoplastic effects were not reported and assumed to have not been investigated.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Quest *et al.*, 1984
Study population	50 rats/group/sex, 300 total.
Exposure method	Discontinuous whole body inhalation exposure (4,985 or 9,891 ppm).
Critical effects	Respiratory system; squamous metaplasia (males and females), epithelial hyperplasia (females only) and inflammation (males only) of nasal cavity.
LOAEL	4,985 ppm (8,570 mg/m^3)
NOAEL	Not observed
Exposure continuity	6 hr/day, 5 days/week
Exposure duration	2 years
Average experimental exposure	890 ppm for LOAEL group
Human equivalent concentration	190 ppm (gas with extrathoracic respiratory effects, RGDR = 0.21, based on BW = 305 g, MV = 0.21 L/min, SA(ET) = 15 cm^2)
LOAEL uncertainty factor	3 (low severity)
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	2 ppm (2,000 ppb, 3 mg/m^3, 3,000 $\mu g/m^3$)

Strengths of the propylene REL include the availability of a long-term, controlled exposure study in large groups of experimental animals that included extensive histopathological analyses.

Lifetime exposure of rats and mice to propylene resulted in adverse effects in the nasal cavity of rats at both exposure levels. Therefore, a NOAEL was not observed. However, the effects observed were mild.

Other weaknesses of the database for propylene include the lack of lifetime toxicity studies in any non-rodent species. Also, no long-term human toxicity or epidemiology studies were located in the literature. Human pharmacokinetic studies to compare with experimental animal pharmacokinetic studies were absent. Another uncertainty is the lack of reproductive and developmental toxicity studies. A comprehensive multi-generation study in an experimental animal species would enhance the development of a propylene REL.

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CHRONIC TOXICITY SUMMARY

PROPYLENE GLYCOL MONOMETHYL ETHER

(1-Methoxy-2-propanol; 1-methoxypropanol; Propapsol solvent M)

CAS Registry Number: 107-98-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**2,000 µg/m^3** U.S. EPA RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC
Critical effect(s)	CNS effects (mild, reversible sedation) in rabbits
Hazard index target(s)	Nervous system

II. Physical and Chemical Properties (HSDB, 1995)

Molecular formula	$C_4H_{10}O_2$
Molecular weight	90.14
Description	Colorless liquid
Specific gravity	0.962 @ 20° c
Boiling point	118-118.5°c
Melting point	-96.7°c
Vapor pressure	11.8 mm Hg @ 25°C
Solubility	Soluble in water, methanol, ether, and other organic solvents
Conversion factor	1 ppm = 3.69 mg/m^3 at 25° C

III. Major Uses or Sources

Propylene glycol monomethyl ether (PGME) is used as a solvent for cellulose, acrylics, dyes, inks and stains (HSDB, 1995). Thus, the primary use of PGME is in lacquers and paints. Use of PGME is anticipated to increase due to its low systemic toxicity.

IV. Effects of Exposures on Humans

No reports or studies of human toxicity following chronic exposure to PGME were located in the literature. Slight eye irritation was reported by two of six human volunteers exposed to 100 ppm PGME for 2 hours (Stewart *et al.,* 1970). These subjects were exposed for a total of 3 1/2 hours during which no decrement in visual acuity, coordination, neurological responses or reaction time was measured. The same experiment exposed 23 subjects to 250 ppm PGME. After 15 to 30 minutes of exposure, 8/23 reported eye irritation and 3/23 reported throat irritation; lacrimation was observed in 3/23 subjects. Three subjects each reported one of the following symptoms: irritation, headache, and nausea. While the subjects frequently reported the odor to be objectionable upon first entering the chamber, the odor was usually undetectable by the end of the exposure. Clinical chemistry and urinalysis completed following exposure was not altered as compared to pre-exposure measurements.

V. Effects of Exposures on Animals

Male and female rats (10 per sex per concentration) and rabbits (7 per sex per concentration) were exposed by inhalation to 300, 1000, or 3000 ppm PGME 5 hours per day, 5 days per week for 13 weeks (Landry *et al.,* 1983). Relative liver weights were statistically significantly higher than controls in both male and female rats exposed to 3000 ppm PGME. Hepatocellular hypertrophy was observed upon histopathologic examination of high dose females. The authors conclude these effects to be the result of physiologic adaptation rather than a manifestation of toxicity. The key observation in this study was sedation of rats and rabbits exposed to 3000 ppm PGME. The sedative effects were no longer apparent after 1-2 weeks of exposure.

Similar findings of mild CNS depression were observed by Hanley *et al.* (1984). Pregnant rats and rabbits were exposed to 500, 1500, or 3000 ppm PGME 6 hours per day either days 6-15 or 6-18, respectively. During the first 4-5 days of exposure, rats in the 3000 ppm PGME exposure group were lethargic and moderately ataxic. Statistically significant decreases in food consumption and maternal body weight gain were also observed during this period. A statistically significant increase in the incidence of delayed sternebral ossification was observed in the 3000 ppm exposure group. Rabbits exposed to 3000 ppm exhibited mild lethargy during the first 1-2 days of exposure with rapid post-exposure recovery. Overall maternal weight gain during the exposure (days 6-18 of gestation) was statistically significantly lower than controls.

No significant effect on fetal birth weight or on pup survival indices (e.g. proportion of pups surviving to day 3 post-delivery) was noted following exposure of pregnant rats to 200 or 600 ppm PGME 6 hours per day on days 6-17 of gestation (Doe *et al.,* 1983). Male rats were exposed to 200 or 600 ppm PGME 6 hours per day for 10 consecutive days. No significant effects on testicular weight or pathology were observed.

Increased liver and kidney weights were observed in male and female rats (10 per sex per concentration) following exposure to 6000 ppm for 7 hours per day, for 81 exposures over a

114-day period (Rowe *et al.,* 1954). No histopathological abnormalities were observed at necropsy.

Ethylene glycol methyl ether (EGME), a structurally-related compound, exerts considerable toxicity on the blood, thymus, testes, and developing fetus. The toxicity of EGME has been linked to its primary metabolite, methoxyacetic acid. Recent comparative toxicity and metabolism studies (Miller *et al.,* 1983, Miller *et al.,* 1984) indicate the relatively low systemic toxicity exerted by PGME is due to its different metabolites. Following a single oral dose of PGME, the key urinary metabolites identified in rats were propylene glycol and the sulfate and glucuronide conjugate of PGME (Miller *et al.,* 1983).

VI. Derivation of U.S. EPA Reference Concentration (U.S. EPA, 1995)

Study	Landry *et al.,* 1983
Study population	Fischer 344 rats (10/sex/concentration); New Zealand white rabbits (7/sex/concentration)
Exposure method	Discontinuous whole-body inhalation (0, 300, 1000, or 3000 ppm)
Critical effects	Mild reversible sedation observed in animals exposed to 3000 ppm PGME. This effect was observed for the first 1-2 weeks of exposure only.
LOAEL	3000 ppm
NOAEL	1000 ppm
Exposure continuity	6 hours per day, 5 days per week
Average experimental exposure	179 ppm for NOAEL group
Human equivalent concentration	179 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Exposure duration	13 weeks
LOAEL factor	1
Subchronic uncertainty factor	10
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.6 ppm (600 ppb, 2 mg/m^3, 2000 $\mu g/m^3$)

Strengths of the PGME RfC include the observation of a NOAEL, and the availability of subchronic exposure studies involving multiple concentrations and species. Major areas of uncertainty are the lack of human data, the small groups tested in the study, and th difficulty in interpreting the significance of apparent acutely toxic effects in deriving a value protective for long-term exposures.

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CHRONIC TOXICITY SUMMARY

PROPYLENE OXIDE

(1-,2-Propylene oxide; methyl ethylene oxide; propene oxide)

CAS Registry Number: 75-56-9

I. Chronic Toxicity Summary

Inhalation reference exposure level	**30 µg/m^3** (U.S. EPA RfC) This document summarizes the evaluation of non-cancer health effects by U.S. EPA for the RfC
Critical effect(s)	Degenerative and hyperplastic changes in the respiratory epithelium of rats
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties (HSDB, 1994)

Description	Colorless liquid
Molecular formula	C_3H_6O
Molecular weight	58.08
Specific gravity	0.83 @ 20° C
Boiling point	34.23° C
Melting point	-112.13° C
Vapor pressure	445 mm Hg @ 20° C
Solubility	Soluble in water, miscible in acetone, benzene, carbon tetrachloride, methanol, ether
Conversion factor	2.38 mg/m^3 per ppm at 25° C

III. Major Uses or Sources

Propylene oxide is used as a fumigant such as in the sterilization of packaged foods. It is also used as a chemical intermediate in the production of propylene glycol and glycol ethers and as a solvent. Propylene oxide is used in the preparation of surfactants and oil demulsifiers (HSDB, 1994).

IV. Effects of Human Exposures

Conclusive data regarding the effects of occupational exposure to propylene oxide were not located.

An epidemiological study examining mortality among workers with exposure to asbestos and several chemicals including propylene oxide identified three deaths due to mesothelioma, a rare cancer associated with asbestos exposure and a statistically significant increase in the number of deaths attributed to forms of heart disease other than ischemia and hypertension (Egedahl *et al.*, 1989). The latter finding was explained by the authors to be the result of differences in diagnostic accuracy between rural and urban, and primary and tertiary medical care settings. A statistically significant decrease in observed deaths were found for all respiratory cancers, cancer of the bronchus and lung, circulatory disease, digestive diseases, cirrhosis and other liver disease, and death due to accidents, poisonings, and violence. These observations may be partially attributed to a "healthy worker effect".

V. Effects of Animal Exposures

Male and female rats were exposed for 124 or 123 weeks (respectively) to 30, 100 or 300 ppm propylene oxide 6 hours per day, 5 days per week (Kuper *et al.*, 1988). Interim sacrifices were performed at 12, 18, and 24 months. Cumulative mortality was statistically significantly different than controls at 115 weeks in rats of both sexes exposed to 300 ppm propylene oxide. Cumulative mortality was also significantly different than controls at 119 weeks in female rats exposed to 100 ppm. However, a contributing factor to the increased mortality in female rats was the presence of mammary tumors. Atrophy of the olfactory epithelium and degenerative changes in the respiratory changes in the respiratory epithelium were observed in both male and female rats following 28 months of exposure to 30, 100, or 300 ppm propylene oxide. Severe hyperplastic changes in the olfactory epithelium was observed in male and female rats following 28 months exposure to 300 ppm propylene oxide. Mild hyperplastic changes were observed in the olfactory epithelium of female rats exposed to 100 ppm propylene oxide.

Rats and mice were exposed to 200 and 400 ppm propylene oxide 6 hours per day, 5 days per week for 103 weeks (NTP, 1985). Survival in mice was adversely affected in all groups exposed to propylene oxide; a statistically significant decrease in survival was observed in male and female mice exposed to 400 ppm propylene oxide. Survival in rats was not adversely affected by propylene oxide exposure. Rats exhibited exposure-related increases in suppurative inflammation of the nasal cavity, epithelial hyperplasia and squamous metaplasia.

Rats were exposed to 1500 ppm propylene oxide 6 hours per day, 5 days per week for 7 weeks (Ohnishi *et al.*, 1988). After 3-4 weeks of exposure the rats exhibited an awkward gait; the rats were ataxic by the seventh week. Histopathological examination revealed axonal degeneration of myelinated fibers of the hindleg nerve and fasciculus gracilis indicating central-peripheral distal axonopathy.

Artificially inseminated rabbits were exposed to 500 ppm propylene oxide on days 1-19 or 7-19 of gestation (Hardin *et al.*, 1983). Maternal toxicity as indicated by a significant reduction in food intake and a significant decrease in maternal body weight gain was observed in both exposed groups. An increased number of resorptions per litter, with no change in total resorptions, was observed in rabbits exposed on days 1-19 of gestation. Sternebral and limb anomalies (considered minor by U.S. EPA and the authors) were significantly increased in the offspring of rabbits exposed on days 1-19 of gestation.

The same study also reported similar findings in sperm-positive rats exposed to 500 ppm propylene oxide on either days 1-16 or 7-16 of gestation or daily for 3 weeks prior to mating and then daily on days 1-16 of gestation. Reproductive capacity was impaired in rats exposed prior to breeding; the number of corpora lutea, implantation sites, and live fetuses were reduced. Those dams exposed pregestationally to propylene oxide also exhibited more resorptions. Maternal toxicity as indicated by decreased food intake and decreased body weight gain was observed in all exposed rats. Significant reductions in fetal body weight and fetal crown-rump length were observed in all exposed groups. An increased incidence of wavy ribs and reduced ossification were observed in the offspring of rats exposed from days 1-16 of gestation.

VI. Derivation of U.S. EPA Reference Concentration

Study	Kuper *et al.*, 1988
Study population	Rats (male and female)
Exposure method	Inhalation (0, 30, 100 or 300 ppm)
LOAEL	30 ppm
Critical effects	Degenerative and hyperplastic changes in the respiratory epithelium
NOAEL	Not observed
Exposure continuity	6 hr/day for 5 days/week
Exposure duration	124 weeks
Average experimental exposure	5.4 ppm for LOAEL group
Human equivalent concentration	1.2 ppm for LOAEL group (gas with extrathoracic respiratory effects, RGDR = 0.23, based on MV = 0.3 m^3/day, SA(ET) = 11.6 cm^2)
LOAEL uncertainty factor	3 (mild effects only observed during last 4 months of exposure
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.009 ppm (9 ppb, 0.03 mg/m^3, 30 µg/m^3)

The major strength of the RfC is the use of a well-conducted long-term multi-concentration study with adequate histopathological analyses. Weaknesses include the lack of adquate human data and the lack of a NOAEL observation.

VII. References

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